SECOND SERIES AUGUST 1939 VOL. 15, NO. 8

BULLETIN OF THE NEW YORK ACADEMY OF MEDICINE

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Published monthly by THE NEW YORK ACADEMY OF MEDICINE
2 East 103 Street, New York

Entered as second-class matter, February 3, 1928, at the Post Office at New York, N. Y., under the Act of August 24, 1912. Subscription $3.00 per year. Single copies, 50 cents

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BULLETIN OF
THE NEW YORK ACADEMY
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AUGUST 1939

OBSERVATIONS ON THE PATHOLOGY OF RICKETS WITH PARTICULAR REFERENCE TO THE CHANGES AT THE CARTILAGE-SHAFT JUNCTIONS OF THE GROWING BONES

Harvey Lecture, February 16, 1939

EDWARDS A. PARK

HISTORICAL

ALTHOUGH rickets was first clearly recognized and described by Glisson[1] in 1650, knowledge concerning the disease remained almost stationary for more than 200 years. It was the monumental contribution to the pathology of rickets by Pommer[2] in 1885 which broke the spell. It laid the foundations of present knowledge concerning the pathological changes and gave correct interpretations of the main features with the exception of the cause of the accumulation of the proliferative cartilage. Since the appearance of Pommer's work, the most important contribution has been that of Schmorl[3] (1909), although his service was to supply sound judgments and points of view rather than new observations or conceptions. A distinct advance followed the experimental production of rickets in animals by Sherman and Pappenheimer[4] (1921) and McCollum, Simmonds, Shipley and Park[5] (1921). The splendid

recent studies by Dodds and Cameron,[6] which have yielded greatly needed precise information, were performed on the rat. Discoveries in other fields have had influence in the interpretation of the pathological changes. We refer in particular to the work of Iversen and Lenstrup[7] (1920), and Howland and Kramer[8] (1921), which disclosed the characteristic deficit in the inorganic phosphorus of the blood and to the work of Holt, LaMer and Chown,[9] Shear and Kramer,[10] Logan and Taylor[11] and others, on the nature of the deposition of mineral matter in bone and the principles involved. The discovery that rickets is a deficiency disease depending on a lack of vitamin D (Mellanby,[12] McCollum, Simmonds, Becker and Shipley[13]) is the most fundamental of all, but it has not contributed directly to the elucidation of the pathology.

The Fundamental Chemical Disturbance

The pathological changes depend on and hence follow a change in the chemical structure of the blood. Most commonly the inorganic phosphorus has fallen to a subnormal concentration, less often the calcium, occasionally both. The result is a depression in the Solubility Product (S.P.) which governs the precipitation of calcium phosphate from the blood (lymph) into the cartilage and bone.* When the S.P. falls below a certain critical value, lime salt deposition in bone and cartilage becomes irregular and, if the value is low enough, deposition stops altogether. The failure in lime salt deposition is responsible for the weakness of the bones. This, in turn, results in the development of the well known deformities of the disease and at the same time is the cause of almost, if not all, the histological changes. The first demonstrable pathological change in rickets is the failure of lime salt deposition in the proliferative cartilage of the epiphysis and in newly forming bone.

The Changes in Bone**

If the rachitic process is of sufficient severity, bone is formed without lime salts. Bone free from lime salts is known as osteoid, i. e., osteoid is the organic part of bone without the inorganic. Since in endochondral

* We speak of the S.P. as a symbol, standing for the general chemical conditions in the blood (lymph) which determine the deposition of calcium phosphate. We are aware not only that its chemical expression is uncertain but also that its postulation is not entirely justifiable at the present time.

** In all descriptions the bone is conceived of as standing on end with the epiphysis upwards. Hematoxylin and eosin stains are referred to throughout.

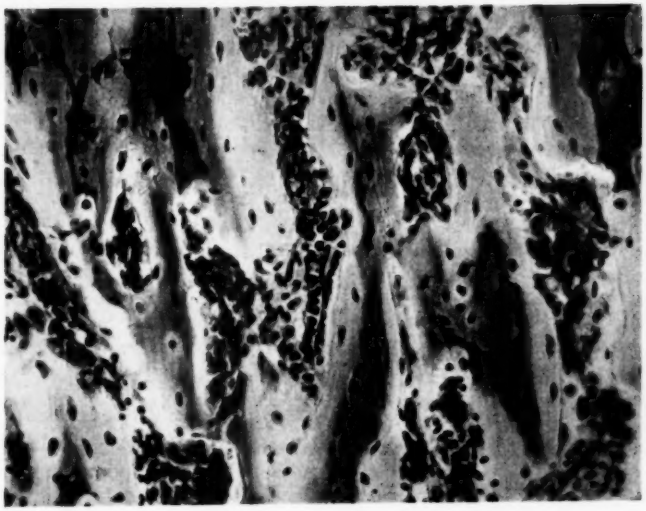

Fig. 1—Photomicrograph (high power view) from a microscopic section, taken from upper end of tibia of the rat.
The bone marrow lies between the trabeculae. The black areas in the trabeculae represent the cores of the original framework of calcified matrix substance of the cartilage on which the osteoblasts settled and formed bone. The gray represent the lime salt containing part of the trabeculae formed before the rickets began; the white borders, the osteoid formed under the influence of the rickets.

ossification new bone forms always on a nucleus or core of old bone or of matrix framework of the cartilage, osteoid always makes its appearance as a surface covering of the trabeculae or matrix framework (Fig. 1). It stains differently from bone that contains lime salts and in that way can be differentiated from the latter. In histological sections, which of course represent single planes, the osteoid coatings always appear as borders (staining pink with eosin) to the lime salt containing trabeculae (staining bluish gray with hematoxylin) or to the matrix substance of the cartilage (which, if calcified, stains a deep blue).

Osteoid is not peculiar to rickets; it develops in the course of normal growth, for, when new bone forms in the healthy individual, it is entirely devoid of lime salts. The lime salts deposit in it later. Thus, under normal conditions, one finds trabeculae with borders of osteoid. In the most rapidly growing bones, those of young prematurely born infants,

osteoid borders are numerous and of considerable breadth. In contrast, in infants suffering from wasting diseases which interfere with osteoblastic activity, as they very probably do with cellular activity in general, osteoid borders may not be found at all, or, if found, are very thin. In the older child in whom growth has waned and in the adult in whom growth takes place only to the extent necessary to counterbalance destruction, osteoid is entirely lacking or at best poorly developed. There is, therefore, a wide variation in the amount and thickness of osteoid coverings under normal conditions, explicable on the basis of variations in the rate of bone growth.

The difference in the osteoid in rickets and the normal state is entirely one of degree. In rickets the osteoid borders are both wider and more generally distributed than normal. The histologist, searching for rickets, scans the shaft, to see if osteoid is in excess. If the osteoid borders appear abnormally broad and abundant, he feels confident that the disease exists.

Schmorl[3] regarded excessive amounts of osteoid in the shaft essential for the diagnosis of rickets and considered it the earliest as well as the most reliable sign of the disease. We are certain, however, that an excess of osteoid is not an invariable characteristic, for we have repeatedly found instances in which it was absent in infants having scurvy, tuberculosis or other wasting diseases, although indubitable evidences of rickets were present at the cartilage-shaft junctions. Proliferation of the cells in the cartilage is responsible for growth of the bone in length; osteoblastic activity in the shaft is responsible for growth of the trabeculae and cortex in thickness. The two processes are, to an extent at least, independent. When osteoblastic activity stops, while growth activity in the cartilage continues, the formation of osteoid borders in the cancellous tissue of the shaft and in the cortex ceases altogether, but the abnormal developments in the cartilage continue. It is wrong, therefore, to conclude that the presence of osteoid in the shaft is absolutely necessary for the diagnosis of rickets, although we admit a certain sense of insecurity if it is not present. Sometimes, in states of malnutrition, when osteoid is almost entirely absent, one can find here and there bits of it having such thickness as to fix the presence of rickets. Sometimes, the osteoid borders are not broader than normal but are so numerous as to establish the rachitic state. Schmorl[3] pointed out that osteoid is especially developed in those parts of the skeleton which are

particularly subject to mechanical strain and hence to rapid growth. In general, however, the distribution of osteoid is fairly even. At the upper end of the ulna, for example, where cartilaginous growth is so slow that rickets may not show itself at all at the cartilage-shaft junction, the osteoid borders in the cancellous tissue of the shaft will be found as well developed as at the ends of the fast growing ribs. Oftentimes, osteoid is found in the cortex, when it is practically absent in the cancellous tissue. One must be careful, however, in making the diagnosis of rickets from the presence of osteoid in the cortex alone, because in rapidly growing bones, in particular those of prematurely born infants, the osteoid borders are apt to be wide in that location. In some cases of rickets we have found the widest osteoid borders in the trabeculae close under the cartilage, in others at a distance in the shaft. In osteomalacia (the rickets of the adult) the only characteristic sign of the disease is the presence of abnormal amounts of osteoid in the shaft and in rickets in the older child its presence may be the sole evidence of the disease, since growth of the cartilage is occurring too slowly for rickets to show at the cartilage-shaft junction. At the ends of the long bones where cartilaginous growth is very slow even in very young infants, the disease must be recognized by the presence of excess osteoid.

In summary we can say that the presence of osteoid in excess is a cardinal sign of rickets and is pathognomonic of the disease. It is the only sign of the disease in osteomalacia and may be the sole sign in the older child. In the prematurely born infant it is often difficult to be certain that an excessive development of osteoid may not be the result of unusual growth activity. The absence of osteoid does not mean that rickets cannot be present.

Does halisteresis occur in rickets? The question has been much debated whether halisteresis ἅλς [salt] and στέρησις [deprivation]—the withdrawal of lime salts from the organic matrix—occurs in rickets. It is of paramount importance to the histologist to know whether to regard osteoid borders as invariably indicative of formation without lime salts or whether they may represent old bone out of which the lime salts have been dissolved. Such distinguished students of rickets as von Recklinghausen[14] and M. B. Schmidt[15] have held that halisteresis occurred in rickets and osteomalacia, whereas others, notably Pommer[2] and Schmorl,[3] have denied the possibility. The more we have studied rachitic bone, the more we have been convinced that halisteresis does

not take place. Apparently Nature's method of obtaining calcium from bone is not to dissolve it, leaving the organic matrix behind, but to break down the organic matrix at the same time that the mineral content is released. Chemists annoy histologists when they speak of decalcification of bone, as if bone were not a living tissue but were composed entirely of inorganic material subject to the laws of the test tube. Even if lime salts are dissolved by some chemical agent, perhaps an acid elaborated by the bone cells, it is necessary to think of the organic matrix, in which the lime salts are imbedded, as being dissolved or disintegrated at the same time. Schmorl[3] made the observation that in areas in which destruction of bone was taking place the leukocytes contained granules of calcified matter.

The distribution of osteoid and its probable significance. Osteoid is not spread evenly over the surfaces of the trabeculae like the chocolate coating of a candy, except possibly over limited areas in some places in the cortex. On the contrary it appears on the surfaces of the trabeculae only here and there. A remarkable feature about osteoid formation in rickets is the complete irregularity of its distribution. Often osteoid borders are present on both sides of a trabecula. As commonly, an osteoid border is found on one side, perhaps of a very thin trabecula, and an area of destruction on the other side, or areas of osteoid formation and of destruction lie side by side (Fig. 2). The only possible explanation of the close intermingling of new bone formation (so easily recognized in rickets because the newly formed bone is osteoid) and old bone destruction is that mechanical conditions are the determining factors. The common occurrence of osteoid on one side of a trabecula and a destructive process on the opposite side is exactly what would be expected, if pressure stimulated new bone formation and tension exerted no influence at all or perhaps was actually destructive. The occurrence of osteoid and areas of bone destruction side by side might also be anticipated, on that hypothesis, if the sinuosity of the trabeculae is taken into consideration. The theory that pressure causes new bone formation and tension is without effect has already been advanced by Jansen.[16]

Is bone destruction increased? The reason that the bones become so weak in rickets is that old bone, i. e., the old lime salt containing bone antedating the advent of rickets, undergoes surface disintegration while the new bone formed, being osteoid, does not possess strength on account of its lack of lime salts. The reason that rachitic bone appears

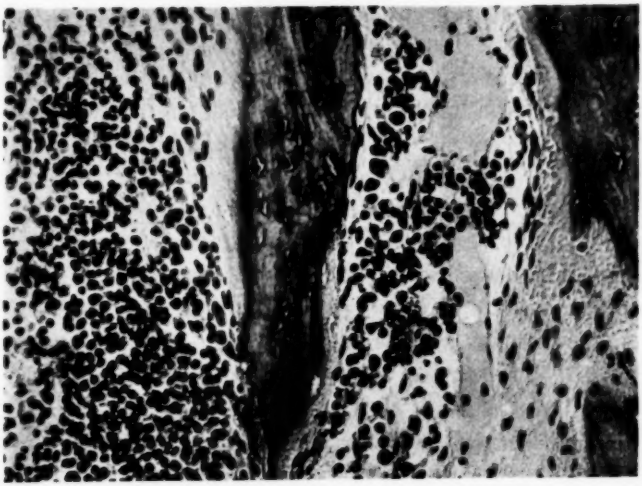

Fig. 2—Photomicrograph (high power view) from a microscopic section, taken from rib of A. J. (No. 948) aged four months.
In the center is a trabecula. On the left hand side of it an osteoid border becomes thinner, as it descends, and finally stops altogether. Just below where it stops is an area of destruction. Thus on the left side one finds abrupt transition from formation to destruction. On the opposite (right) side the reverse condition is present, namely, bone destruction above, osteoid formation below. The illustration is presented, in order to show how closely new bone formation, which can be traced so beautifully in rickets, and old bone destruction are intermingled.

so rarefied in the x-ray film is because the old lime salt containing bone is reduced whereas the newly formed bone casts little shadow.

The question has been debated whether in rickets destruction of old lime salt containing bone is increased. The histologist is not the one capable of giving final judgment. All that he is able to contribute is the *impression* that the areas of resorption, as seen under the microscope, are or are not more numerous than he would expect under normal conditions. The measurement of the density of rachitic bones by means of the x-ray indicates that the destruction of lime salt containing bone must have been extreme but does not exclude prolonged action of normal forces. In metabolism studies in rickets, however, the balance of calcium is rarely negative. From this fact one can infer that the destruc-

tion of old bone can only rarely be of extreme degree. In hyperparathyroidism, in which we know that bone destruction is greatly increased, the calcium balance is regularly negative (Bauer, Albright and Aub[17]) and the urinary excretion of calcium is increased. In rickets the urinary excretion is unaffected or becomes diminished (Orr, Holt, Wilkins and Boone[18]). The loss is from the bowel, due almost entirely to failure in absorption (Telfer[19] and Nicolaysen[20]). Hamilton and Highman[21] have shown that in the rabbit in which rickets has been produced by a low phosphorus diet the actual quantity of calcium contained in a given bone becomes reduced, in spite of continued growth in length. We can conclude that usually in human rickets destruction of bone cannot be greatly increased but undoubtedly may be increased in the severest developments of the disease. However, such factors as the inactivity resulting from weakness or general malnutrition may take part in the process.

Changes at the Cartilage-Shaft Junction

Before we take up the changes at the cartilage-shaft junction we must make clear that rickets occurs in all degrees of severity. It may be so mild as to be scarcely distinguishable by any means or so severe as to threaten the integrity of the skeleton. Chronic rickets with lime salt depositions occurring sporadically is very common; it may last for years. A description of the lesions at the cartilage-shaft junctions in severe forms of the disease would not fit the mild or the chronic, although the underlying disturbance remains the same in all. We must also bring out the fact that rickets affects the growing ends of bones in different degrees according to the rate of growth of the cartilage. For example, the slow growing upper end of the ulna will show little evidence of the disease at a time when the rapidly growing anterior end of the eighth rib shows most pronounced effects. A description of the former would not apply to the latter, although the principles in operation are the same.

The earliest manifestations. The first signal of rickets at the cartilage-shaft junction is failure in the usual lime salt deposition in the layer of cartilage close to the shaft. Defective calcification at the cartilage-shaft border and osteoid formation in the shaft develop together. They are the first and the essential manifestations in the skeleton. As the result of the loss of the normal support furnished by the lime salts the tissues bordering on the cartilage-shaft junction give way and are pressed

together. Compression is not, however, a constant manifestation either in all individuals or in all bones. The circulation at the cartilage-shaft border becomes disarranged; the orderly invasion stops. The proliferative cartilage begins to increase in amount. Its swelling can sometimes be actually demonstrated. Presently a disorderly invasion commences. It may, then, be observed that in certain places along the cartilage-shaft border, where the cartilage is touched by the blood vessels curious changes develop in it.

Considering the matter from the practical viewpoint, the pathologist searches to see if there are small gaps in calcification, and if in places the deposition is of an abnormally light or fragmentary character, or if it extends less than the wonted distance into the substance of the cartilage; also, if the capillaries are abreast of its furthest outposts or if some have even begun to enter the uncalcified cartilage beyond. He inspects the advance fringe of calcified matrix framework to learn if the spicules are bent or broken, and examines the cartilage cells closest to the shaft for evidences of compression or displacement. He tries to estimate if the fully developed cartilage cells are in excess. Finally he looks at the cortex and cancellous bone with the greatest care, in order to form an opinion whether the osteoid is in excess of normal.

Wolbach[22] states: "The first histological evidence of rickets is the absence in whole or in part of the layer of clear cells and the consequent absence of ingrowth of capillaries." Schmorl[3] regards connective tissue formations immediately under the cartilage as one of the earliest signs.

We shall now describe the changes which mark the beginning of rickets, as we see them, and shall trace their development, trying to explain why they occur, even though essential facts are lacking.

The disturbance in calcification. By killing young rats in succession it is possible to trace the disturbance in calcification at the cartilage-shaft junction. Within twenty-four hours after the substitution of the Steenbock-Black rickets-producing diet (Steenbock and Black[23]) it is manifest, for the fringe of the framework of calcified matrix extending into the cartilage between the cells has already given way. According to Dodds and Cameron[6] deposition first fails in the thinner parts of the matrix framework of the cartilage. In the more massive parts it continues but occurs most constantly at the intersections. It gradually diminishes and at the end of two or three weeks ceases altogether. The defects in calcification are very small at first.

The disturbance in lime salt deposition at the cartilage-shaft junction in the infant develops in a similar manner. In the fast growing ribs of the young infant one finds that here and there the spicules of calcified matrix framework are thin and in spots two to four or more cartilage cells in diameter, the lime salts have failed to precipitate altogether or have fallen in thin, fragmentary fashion. Under normal conditions, lime salts do not deposit in the thin matrix partitions separating the cartilage cell columns of the bundles from each other but they do deposit in the more massive main partitions which lie between individual columns and bundles of columns. It is common to find that calcification of a main partition may be lacking here and there or that it has occurred only along the border of the partition where the latter touches the cartilage cells, or that the deposition is represented only by fragments, in histological preparations, at least, appearing to be completely disconnected from the rest of the network. The calcification may extend only a short distance into the proliferative cartilage. When one finds this, he is at a loss to know whether it had never extended the normal distance, or whether it had stopped advancing and the marrow vessels had caught up with it. The spots of defective calcification are only a few cells wide and are irregularly scattered exactly as in the rat.

In bones which are growing slowly no defects in lime salt deposition may be apparent for some little time after rickets shows itself plainly elsewhere. They develop gradually. They may be small, when first noticed, but are often fairly large. Underneath them it is common to observe distended blood vessels.

If the rickets continues and invasion of the cartilage occurs, the blood vessels keep carrying away the lime salt deposits and the defects become wider.

It is not possible to discover by histological methods any change in the cartilage which fails to calcify in order to account for the failure. We shall return to the subject of calcification further on.

Compression. As in the case of calcification, development of compression at the cartilage-shaft junction can be readily followed in the rat but not in the human being. At the upper end of the tibia of the rat it is already well developed at the end of twenty-four hours on the Steenbock-Black rickets-producing diet. The compression involves the lowermost cells of the proliferative cartilage and the interdigitating fringe of calcified matrix framework. Both the capsules which are as yet unopened

by capillaries and those which have just been opened are affected. The collapse of the cell capsules may be partial or complete. If the collapse is incomplete, the spicules of calcified matrix substance are bent or buckled or may be fractured and the cell capsules are pressed into a variety of shapes. If the collapse is complete, the unaffected blue staining proliferative cartilage rests against the end of the shaft with the layer of collapsed tissues between. In the severest degrees of compression the intracellular spaces are obliterated and the spicules are flattened out, so that they lie horizontally. They may be impacted into or driven against the soft cartilage. The compression zone is rarely continuous across the cartilage-shaft junction and in the case of the upper end of the tibia, which is the bone we have studied, the peripheral parts remain free. Indeed, in that bone at the anterior end of the cartilage-shaft junction cartilage and shaft often are torn apart. Commonly the compression occurs in spots alternating with uncompressed areas. As the rickets progresses, collapse continues. The tissues which are freshly formed under the rachitic influence keep giving way, so that one finds strata of compressed tissues at higher levels in the shaft. But the original stratum of compression persists and can be readily identified for two or more weeks in the substance of the shaft. From it one can locate the starting point of the rachitic process.

In the human being collapse at the cartilage-shaft junction also occurs very early and may be exactly like that just described in the rat (Fig. 3, *a*, *b*, *c* and *d*), that is, both the layer of large swollen cartilage cells in contact with the shaft and the fringe of calcified matrix substance, which has extended in between them, are involved. As in the rat, the cell capsules may be partly collapsed, so that the intracellular spaces remain partially open, or they may be completely flattened. The spicules of the fringe may be simply bent to one side or extensively buckled or fractured or flattened so that they lie horizontally. As in the rat, at the extreme periphery compression is not usual. If no lime salt deposition has taken place in the cartilage in contact with the shaft, the cartilage alone is affected in the compression process. In an illustrative specimen in our possession the compression of the under surface of the proliferative cartilage was at least fifteen cells deep. The ends of the trabeculae were driven into the soft cartilage. At the points of impaction the cartilage cells were squeezed flat and had the appearance of fibrous connective tissue with nuclei running horizontally. In the spaces between the trabe-

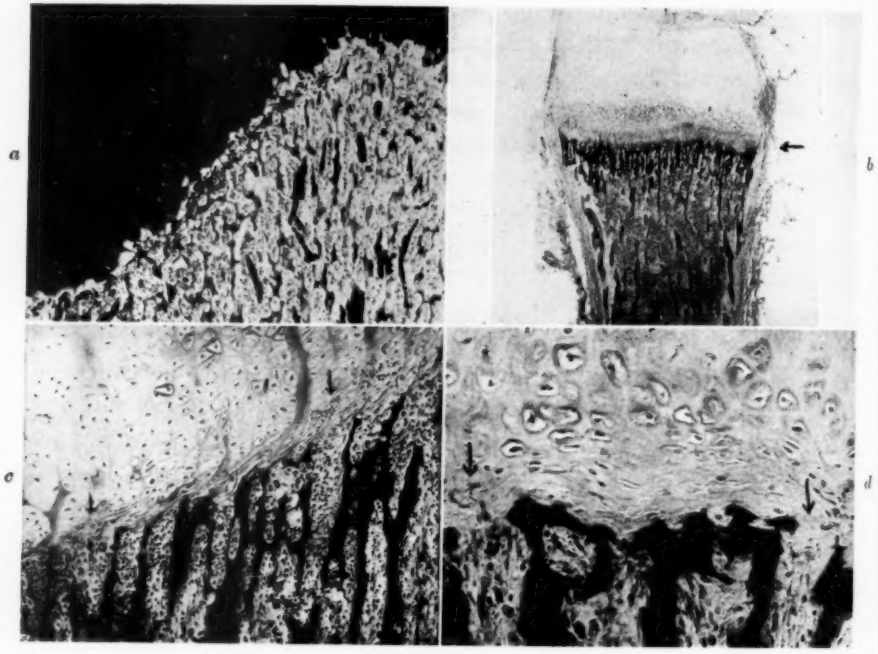

Fig. 3

Fig. 3—*a*. Photomicrograph (low power view) from a microscopic section of the upper end of the tibia of the rat killed twenty-four hours after the substitution of the Steenbock-Black rickets-producing diet for the stock diet.

The picture is presented in order to show that, already, collapse of the fringe of framework of calcified matrix substance has taken place. The crushed fringe embraced not only the cartilage cell capsules which had just been penetrated but also the capsules of the lowermost fully developed cartilage cells which were in process of being attacked.

Fig. 3—*b*. Photomicrograph (low power view) from a microscopic section of the lower end of the ulna of W. H. (No. 1073) aged two months.

The picture shows the bending and fracture of the fringe of the framework of calcified matrix substance. The condition in this infant corresponds exactly to that just shown in the rat in Fig. 3, *a*.

Fig. 3—*c*. Photomicrograph (low power view) from a microscopic section of the rib of J. R. (No. 1015) aged two months.

The picture shows the compression, which is resulting in stratification, of the lowermost cartilage cells, those in contact with the trabecular framework. The ends of the spicules of the trabecular framework are bent and everted to the right. At the left (the point indicated by an arrow) pocket formation has commenced and at the top of the pocket

culae the cartilage bulged downwards into the shaft and had a looser, more nearly normal arrangement. If the rickets continues, the weak tissues forming under its influence keep on giving way from time to time as in the rat. But these collapses are not conspicuous unless lime salts are present to mark the pattern.

Slight degrees of compression are much commoner than the severe ones described. The cartilage capsules next the shaft are oval or show a variety of irregular shapes and often are squeezed out of line, so that the columnar arrangement is gone. Also, as in the rat, the compression areas are scattered and seem to have a special connection with certain trabeculae or trabecular groups.

Collapse at the cartilage-shaft junction, as already pointed out, does not occur universally in rickets. It is a phenomenon, as might be imagined, dependent on the combination of rapid growth, severe rachitic state and pressure. It will not be found at the cartilage-shaft junctions at which growth is very slow. We find it chiefly at the fast growing ends of the long bones in young infants in whom severe rickets has developed suddenly. Compression signs will not be found at the slow growing ends of the bones because their strength is so little impaired. It is remarkable, however, if one examines with great care the entire breadth of the cartilage-shaft junction, in particular the points at which the trabeculae abut on the cartilage, how often slight degrees of compression are present.

The cause of the compression is evident enough. Apparently the extension of the lime salt deposition into the framework of matrix substance of the cartilage is designed not alone to guide the invading capillaries but

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is a fragment of calcified matrix substance. At the point on the right indicated by the arrow a blood vessel has begun to work its way into the cartilage.

Fig. 3—*d*. Photomicrograph (high power view) from a microscopic section of the rib of F. R. (No. 165) aged two years.

The picture shows the most extreme compression of the bottom-most part of the proliferative cartilage. The compressed tissue is ten to fifteen cells deep. The lacunar spaces are represented by slits. The advance fringe of the framework of calcified matrix substance has been fractured and bent back with the crushing of the cartilage cells in the general collapse. The reason that the framework does not extend into the substance of the cartilage is because it has been flattened out. Formerly it did extend into the cartilage between the cell columns. At the two points indicated by arrows invasion is commencing. Between these points in the plane of the section vessels are prevented from reaching the under surface of the cartilage as the result of the trauma. Compressed cartilage, such as is exhibited, offers a formidable barrier. The columnar arrangement of the cartilage cells is entirely gone.

also to give support to the large swollen cartilage cells bordering on the shaft. Obviously the capsules of these cells are unable, unsupported, to withstand pressure. It is noteworthy that the compression is limited to the lowermost cells, those in contact with the shaft. The weakening process, therefore, does not seem to be the result of aging but rather of the influence of the approaching marrow elements. If the cartilage cell is viewed as a sort of bladder which, when squeezed, is readily flattened out but is prevented from bursting by the circular fibers in its capsule (Benninghoff,[24]) one can understand the variety of form and displacement. The observation that, except in very severe cases, the compression occurs only in localized areas is most important, for the establishment of barriers at the cartilage-shaft junction has a great influence in determining the irregular invasion of the cartilage which presently will be discussed.

Elongation of the zone of proliferative cartilage. All pediatricians know that the increase in length of the clear space between the end of the shaft and the nucleus of ossification of the epiphysis, as seen in the x-ray film, is a sign of rickets. Study with the microscope shows that the tissues composing the clear space are proliferative cartilage and trabeculae composed of osteoid covered cores of uncalcified matrix framework, sometimes containing cartilage cell inclusions (chondro-osteoid trabeculae*), with blood vessels, marrow and connective tissue cells between. The proliferative cartilage occupies the upper part and is greatly in excess of the normal and in the earlier stages of the disease forms the major part of the transparent tissue. The chondro-osteoid trabeculae naturally are found on the shaft side. They vary in quantity very much, increasing as the rickets becomes older. The excess of proliferative cartilage was thought by Pommer[2] to be due to increased growth. He conceived that the cartilage cells multiplied faster than normal as a result of stimulation from the combined influence of some toxin and increased vascularity. The true cause, namely, failure on the part of the forces of the shaft to invade the proliferative cartilage and to build it over into shaft was clearly recognized by Schmorl,[3] although his pet proof, based on the distance apart of the transversely directed blood vessels, rests on an entirely erroneous conception of the blood supply. The proliferative cartilage increases in amount merely because it accumulates. Incidentally, Jahn[25] and Schmorl and Lossen[26] demonstrated that the proliferative cartilage in

* We use the term chondro-osteoid trabeculae whether the core substance on which osteoblasts have built is composed of uncalcified cartilaginous matrix framework alone or in addition contains cell inclusions.

the non-rachitic rabbit would increase in mass, if the circulation of the shaft were prevented from reaching it.

In the rat the part of the proliferative cartilage responsible for the increased length, is the zone of large, fully developed cells. Dodds and Cameron[6] find that the total length of the proliferative cartilage at the upper end of the tibia in rats fed the Steenbock-Black rickets-producing diet for from three to eight weeks may be increased to fifteen times the normal (Dodds[27]) and that the number of cells in the affected zones vary from eighty-eight to one hundred and forty-five, as compared with a normal of about four. Dodds and Cameron[6] find also that the cells have a decreased vertical diameter; they are shorter (flatter) than normal, a phenomenon attributed to defective formation but perhaps due in part to compression. The topmost zone, that of "reserve cells" and the zone of flat cells below, designated "the zone of flattened cells and cell multiplication," showed essentially no changes except that mitosis appeared to be diminished in the later stages of the disease.

Dodds and Cameron's[6] observations on growth of the tibia of the rat in rickets are interesting. They found that the growth in length was retarded from the beginning but continued for about three weeks, and that it then virtually stopped. They ascribed the retardation and stoppage to two factors, first, the diminution in cell multiplication, and, second, the production of cells having a smaller vertical dimension. In our experiments with the rat the tibia stopped growing and the shaft proper, lengthening by the eleventh day and in some instances even earlier.

In the puppy the zone of proliferative cartilage may become enormously increased and it may also be much increased in the rabbit (Fig. 4). That the proliferative cartilage can be in great excess in rickets in the case of the human being is common knowledge. Dodds and Cameron's[6] observations on the rat probably apply to the human being. The increase in the length of the proliferative zone is due to an increase in the number of large fully developed cuboidal cells which are the products of cell multiplication. The zones of cell multiplication are not increased in size. It is also probable that in human rickets multiplication of the cartilage cells becomes retarded. We say this because of the well-known fact that, if rickets persists over a number of years, retardation of growth may become extreme. Dodds and Cameron's[6] observations that in the rachitic rat, cell division in the proliferative cartilage dwindles, is of fundamental importance since it shows actual growth processes are affected.

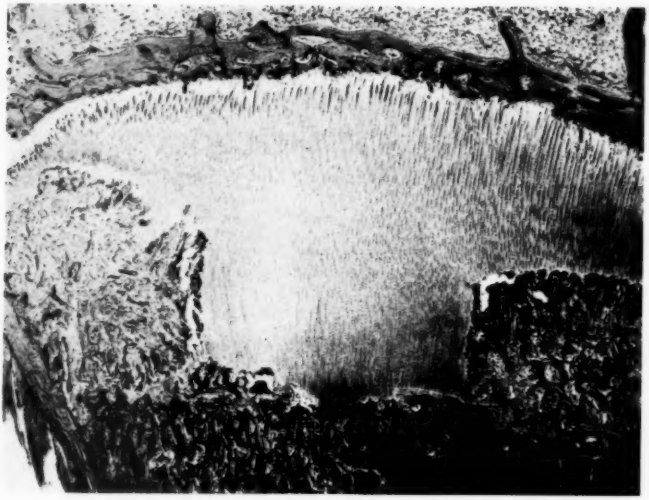

Fig. 4—Photomicrograph (low power view) taken from the microscopic section of the upper end of the tibia of a rabbit in which rickets has been produced.
The picture is shown in order to illustrate the great broadening of the proliferative cartilage which occurs in rickets and also the irregularity of the invasion. At the sides blood vessels have extended far into the proliferative cartilage and on the left have advanced almost to the normal limit of penetration. The reason that the central portion of the proliferative cartilage remains essentially intact is that it has been protected by a barrier of crushed tissues composed of both cartilage cells and matrix framework.

Swelling of the proliferative cartilage. The evidences of swelling of the proliferative cartilage can occasionally be found in the human being at the fast growing bone ends. They consist in a deflection outwards of the spicules in the peripheral part of the fringe of calcified matrix substance, while the more central parts retain their vertical direction. Also, the columns of cartilage cells at the extreme periphery bulge above the junction with the shaft, as if prevented from expanding at the shaft level by their attachment.

Invasion of the cartilage. As long as lime salt deposition in the proliferative cartilage is preserved, normal invasion continues, that is, individual capillaries continue to attack individual cell columns or column groups. But as soon as it becomes disorderly or stops, the focal type of

invasion of the proliferative cartilage, so characteristic of rickets, sets in. This type of invasion depends on failure in lime salt deposition at the cartilage-shaft junction. It commences much sooner, therefore, in severe than in mild rickets. Indeed, as Dodds and Cameron[6] point out, the normal kind of invasion may be approximated indefinitely, if the rickets is mild enough. In the rat when the Steenbock-Black rickets-producing diet is substituted for the stock ration, irregular penetration appears at the earliest on the fourth day and does not become well developed until the tenth. In contrast, the defect in lime salt deposition and the compression at the cartilage-shaft junction declare themselves within twenty-four hours. A latent period, therefore, is required, for the disturbance in invasion to reach the magnitude necessary for it to become apparent. The same is undoubtedly true in the human being.

In the human being we have found the study of the beginnings of the penetration difficult. Apparently the course is not always the same. If fresh calcium deposition has ceased all along the front, it is common to find that the capillaries have advanced to the level of the furthest deposits and that some are extending out into the cartilage in advance of them. This type of invasion is most commonly seen at the cartilage-shaft junctions of the very rapidly growing bone ends in young infants. Another example of invasion, the one often encountered at the slow growing bone ends, is as follows: At various points in the proliferative cartilage calcification is defective. Beneath the defective areas lie dilated capillaries, often in holes or pockets in the lattice framework. Either the pockets happened to be there or they were created by the blood vessels. In some instances the latter explanation seems probable because a fragment of a spicule of calcified substance protrudes from the cartilage edge or lies free in the pocket (Fig. 5), or because one of the more massive partitions of matrix substance ends at the under surface of the cartilage, as if cut away, instead of being continuous with the lattice formation underneath. The matrix substance of the cartilage in contact with the capillary stains yellow (hematoxylin and eosin preparations) and the loss of power to take the blue color has extended upwards. In some instances, this change does not occur. Adhering to the under surface of the yellow cartilage are a few cells of the connective tissue family, probably mesenchymal cells accompanying the capillary. These are the premonitory signs. In the next stage the vessel has broken into a lacuna or produced an excavation in one of the more massive arms of the matrix

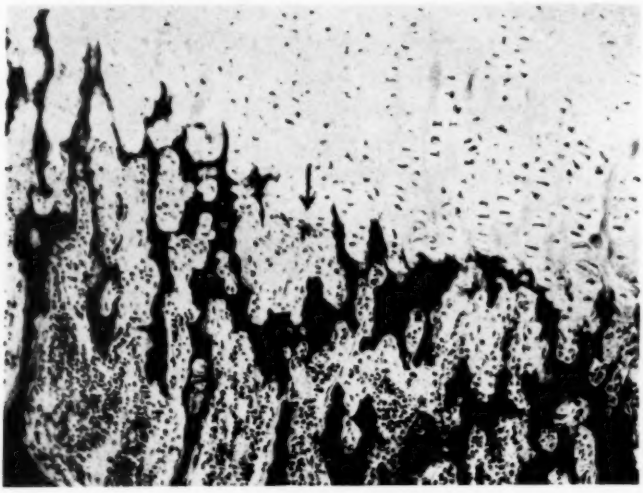

Fig. 5—Photomicrograph (low power view) from a microscopic section of the rib of J. W. (No. 159) aged fifteen months.
The picture shows a pocket in the framework of calcified matrix substance such as the capillary creates when it reaches the under surface of the cartilage and is unable to advance. A fragment of calcified matrix substance can be seen at the top of the pocket. Presumably this represents a remnant which, if death had not supervened, would soon have been carried away. On the under surface of the cartilage which forms the roof of the pocket some cells, presumably mesenchymal cells which accompany the blood vessels, are present but do not show. The cells in the pocket are almost entirely connective tissue cells. It was such accumulations which made Schmorl regard connective tissue formations immediately under the cartilage as one of the very early signs of rickets. The cartilage above the pocket shows the yellow color and other degenerative changes described in the text.

framework. Later one finds that the vessel has made a definite advance into the cartilage substance and the yellow color has extended higher in the matrix framework.

Vessels may pass through the calcified framework and on into the cartilage just as under normal conditions. In some places in which the plane of the histological section makes it possible to trace what has happened one can see broad channels leading through the lattice framework to the under surface of the cartilage and vessels traveling up them and passing on into the cartilage. Obviously vessels break into the cartilage

wherever they can and the eruption need not be attended with abnormal signs.

After the vessels have succeeded in reaching the interior of the proliferative cartilage they seem to grow rapidly. The picture of the invasion process, after penetration of the cartilage has taken place, is best obtained through the study of cleared preparations.* When in the early stages of rickets these are examined, tiny sprouts appear to be growing from the end of the shaft. At a later stage the sprouts resemble small bushes, with respect to stem, branches and rounded outline. When the rickets is advanced, the picture is like this: From the end of the shaft a variable number of bush-like formations protrude. Some have a single stem from which fact it can be inferred that originally a single capillary broke through, others have a number of stems and a broad base, indicating that several capillaries must have broken through together. A great difference in size is noted. Some bushes may be so large that they extend well toward the top of the proliferative cartilage. Side by side with them may be smaller vessels. In yet other places the bud-like outgrowths are just commencing. The bushes are not distributed with any symmetry. The outer side of the upper end of the femur, for example, may show none but the inner side many. They may lie close together in one region and be widely separated in another. In general, even if close, they are separated by transparent cartilage but, if large, which means that the rachitic process must have lasted for a long time, they may meet. Most of them seem to be lying in a vertical direction but some may incline. If one inclines, examination shows that the surrounding cartilage has been displaced out of the vertical direction, presumably from the action of mechanical factors. The inclination of the bush depends on the inclination of the cartilage in which it is growing. The study of cleared preparations brings out the fact in the most striking way that blood vessels break into the cartilage at different times. The variations in size can mean only that penetration was easier at some points than at others.

If the rickets is mild and growth slow, one finds in the transparent preparations only the vessels from the end of the shaft, as just described. But if the rickets is of long duration and severe and the proliferative cartilage has accumulated in large mass, additional vessels, often very large ones, are seen descending from above and also entering from the sides

* The cleared specimens which we have employed are slabs of bone cut longitudinally through the cartilage-shaft junction. They were made transparent with potassium hydroxide, stained with alizarin and stored in glycerin.

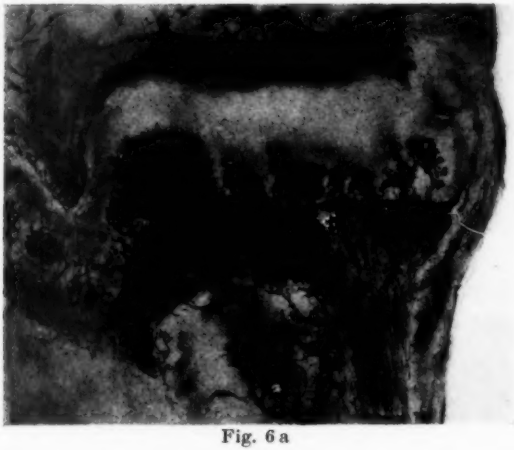

Fig. 6a

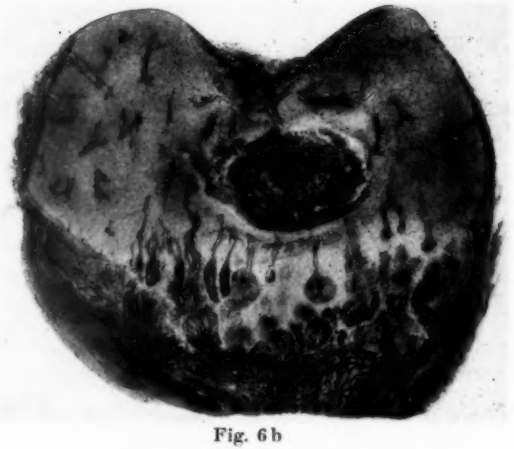

Fig. 6b

Fig. 6—*a*. Drawing from a cleared specimen of the upper end of tibia of a rabbit in which rickets had been experimentally produced. The vessels have been injected with india ink. The vascular bushes, extending from the end of the shaft into the substance of the proliferative cartilage, are beautifully shown. It will be observed that they have single stems. Obviously only single capillaries succeeded in breaking through. With the accumulation of proliferative cartilage which kept furnishing more soil they grew into large bushes. Between the bushes along the under surface of the cartilage are compression barriers which do not show in the drawing.

Fig. 6—*b*. Drawing from a cleared specimen of the lower end of the femur of L. H. (No. 545) aged ten months. The picture shows the vessels protruding from the end of the shaft into the rachitic intermediate zone from below and the descending branches of the cartilage canals extending into it from above. The vessels which have penetrated from the end of the shaft have developed bush-like formations. They vary greatly in size. The variation is explained on the ground of different times of perforation through the barrier of compressed tissues at the cartilage-shaft junction. It will be noted that branching has occurred immediately after penetration. The descending branches of the cartilage canals, on the other hand, have begun to branch only after reaching the zone of fully developed cartilage cells which is the one favorable for growth. Their stems, therefore, appear quite long. On the left hand side one can see the perichondrial vessels arching upwards into the proliferative cartilage and some smaller perichondrial ingrowths are visible on the right side. The effect, in the original cleared specimen, as seen under the dissecting microscope resembled pictures of submarine vegetation.

(Fig. 6, *a*, *b*, *c* and *d*). The mass of cartilage is being invaded from all quarters.

The vessels entering from above have the same general bush-like appearance as those extending upwards from below, but they have much longer stems, that is, they descend into the cartilage for some distance before they begin to branch, whereas the vessels rising out of the shaft branch immediately. They vary in size, just as do the vessels ascending from the shaft, but, unlike the latter, show branching at widely different levels. They are not disposed symmetrically and do not lie in any definite spatial relationship to the shaft vessels. A descending vessel may be opposite an ascending, or a descending may extend downwards between ascending ones. They remain separated from each other by the clear cartilage and in general do not join the upgrowing vessels from the shaft. Particularly in the ribs, when the seat of severe rickets, the descending branches may reach enormous size, extending almost to the shaft. When such is the case, vessels from the shaft are poorly developed.

The vessels entering from the sides seem of minor importance. They usually are small and turn upwards either immediately on entering the cartilage or after penetrating only a short distance. They thus keep fairly close to the perichondrium. Occasionally one is seen growing into the cartilage at right angles to its columns.

We have obtained the distinct impression that the invading vessels tend to avoid each other, as if a negative chemotaxis existed, although in advanced rickets some of them may join. When rickets begins to heal, they grow together with rapidity.

The presence of vessels growing into the cartilage from the shaft is to be expected. But in the normal bone, vessels do not invade the proliferative cartilage from elsewhere. In order to make the origin of the invasion from these new quarters clear, it is necessary to explain briefly the vascular supply of the cartilage in the young child.

What are the cartilage canals? The proliferative cartilage in the normal infant and young child has a blood supply of its own. The vessels composing it, together with their connective tissue adnexa, are known as cartilage canals because of the broad channels which they create in the cartilage substance. They contain an artery and (often two) veins and are surrounded by a thick investment of connective tissue in which run many small branches and capillaries. The canal vessels are branches of the perichondrial vessels. In the rib cartilage canals occur in the rest-

Fig. 6c

Fig. 6d

Fig. 6—*c*. Drawing of cleared specimen of the rib of D. J. (No. 184) aged nine months. It shows quite beautifully the invasion of the cartilage by blood vessels springing from the end of the shaft. The vessels are long and thin. They are separated from each other by transparent cartilage. At the lower half of the central group of vessels chondro-osteoid trabeculae which have been developed about the stems have taken up lime salts. Their true trabecular nature can easily be detected because of their characteristic pattern. They appear black in the drawing. At the left, in the cartilage, close to the perichondrium, is a deposit of lime salts. It lies between vessels which have ascended from the shaft and the perichondrial membrane. Its pattern is rather poorly represented in the drawing, because its texture is so fine as to defy delineation. On the right side, a perichondrial vessel has arched out into the substance of the proliferative cartilage and some of its lowermost branches are growing at right angles into the latter. Just above the vessels is another deposit of lime salts in the cartilage. Its characteristic relationship to the blood vessels does not show particularly well in the drawing.

Fig. 6—*d*. Drawing of a cleared specimen of the rib of L. H. (No. 545) aged ten months. The drawing shows beautifully an enormous accumulation of cartilage in the rachitic intermediate zone and correspondingly enormous descending branches of the cartilage canals, which reach to the shaft. The drawing also shows perichondrial ingrowths on both sides. The enormous size of the descending branches of the cartilage canals and the very large size of the perichondrial vessels is due to the fact that essentially no invasion has taken place from the shaft itself. As pointed out in the text, blood vessels of perichondrial and cartilage canal origin attain great size, only when invasion from the shaft is almost entirely prevented by barrier formation. The drawing also illustrates how the ingrowing vessels, no matter from which side they come, seem to avoid each other. As soon as healing takes place they grow together.

ing as well as in the proliferative cartilage. Those supplying the proliferative cartilage are the ones which concern us. They penetrate the resting cartilage just above the level of the proliferative cartilage, skirt along the top of the latter giving off branches which end there and others which descend vertically toward the shaft. The descending branches, except in rare instances, appear to atrophy after a short distance. The thick surrounding cartilaginous walls, however, diminished and contracted into a band, are prolonged into the shaft. Often the osteoblasts build on it a massive trabecula which in the x-ray film can be seen extending far down into the shaft. It is very difficult to determine how far down blood vessels reach in these descending offshoots. Our general impression is that they extend only a short distance.

The vascular supply of the proliferative cartilage of the long bones having epiphyses is exactly similar to that in the ribs except that in them the proliferative cartilage does not have its private supply system. The vessels extending into it are branches of vessels which cluster around the nucleus of ossification. All the vessels of the cartilage canals terminate in curious bulbous formations. They do not anastomose and are, therefore, end vessels.

The cartilage canals are temporary structures, evidently necessary for nutrition of the cartilage in fast growing centers, for they atrophy and disappear later on in childhood. They are present in the puppy and young rabbit but not in the much smaller bones of the young rat in which diffusion distances are small.

The mechanism of invasion. In the proliferative cartilage of the fast growing epiphyses either single columns of cartilage cells or small groups of columns, forming fascicles, are the units. They are separated from each other by, relatively speaking, *thick* layers of matrix substance which constitute the major or essential framework of the proliferative cartilage. It is in this framework that the lime salts deposit. This framework persists after the cartilage cells have been cleared away by the invading blood vessels and on its surface the osteoblasts settle and build bone. The individual cells of the columns are separated from each other by their capsules and a thin intervening layer of matrix substance. These, fused together, form the intercellular cross partitions. The individual columns of the fascicles have also thin separating layers. These form the thin longitudinal partitions. Unless growth is very slow, lime salt deposition does not occur in them or in the cross partitions and both are destroyed by

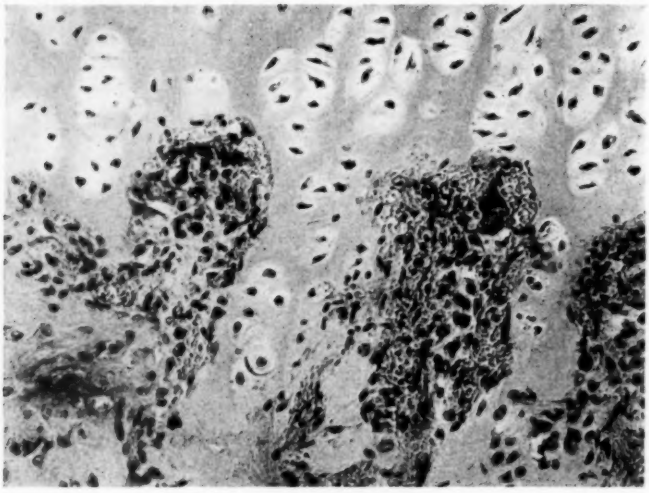

Fig. 7—Photomicrograph (high power view) from a microscopic section of the upper end of the femur of J. W. (No. 957) aged three and a half months.

The picture shows the *en masse* invasion which occurs characteristically in rickets. It is apparent that not only are the cartilage cells being attacked and destroyed but also the matrix framework. On the right side matrix framework denuded of its cells persists but in the center a partition between the vascular outgrowths contains cartilage cells. When osteoblasts settle on these partitions of matrix framework substance with or without cells and form osteoid coverings, the typical chondro-osteoid trabeculae, so characteristic of rickets, are produced.

the invading blood vessels. The course in normal endochondral bone formation, then, is as follows: When a single column of cartilage cells stands in the path of a capillary, the capillary breaking into the lacuna of the nearest cell encounters the cross partition above. After a delay required to overcome its resistance the capillary breaks through into the next lacuna, and so on. If a fascicle of columns lies in front, the capillary, spreading out, attacks the bottom-most layer of cells simultaneously. This process necessitates the destruction of the uncalcified longitudinal partitions between the columns in addition to the cross partitions.

In rickets the method of invasion of the cartilage is similar to that which occurs normally, when a fascicle of cartilage columns is dealt

with, that is, the blood vessel attacks simultaneously a group of cartilage columns and the matrix substance between. However, there is this important difference, that in rickets the capillary (or capillary group) attacks at the same time several different units, i.e., several columns and fascicles together and so encounters the thick matrix walls which separate the units from each other. When invasion of the proliferative cartilage is just commencing it is common in the histological preparation to see a capillary growing against three to four columns of cartilage cells and leaving a correspondingly wide track behind (Fig. 7). In severe protracted rickets one often finds an arc or horseshoe of dilated capillaries, representing the outermost branches of a large vascular bush, attacking simultaneously dozens of columns. With the increase in size of the invading blood vessels this *en masse* mode of destruction of the cartilage proceeds on larger and larger scale. When the invasion has gone on for a long time, one sometimes finds along the invasion surface large holes or cavities, evidently representing the lumina of blood vessels, which may or may not be filled with blood cells. Evidently the surface capillaries of the bush have become large channels (Fig. 8). The mechanism of destruction of cartilage in this *en masse* type of invasion, as seen under the microscope, appears to be as follows: The capsules of the cartilage cells obviously resist the vessels for a time and then one suddenly gives way. The vessel entering the lacuna creates for the moment a small salient at that point, then an adjacent cell capsule gives way, and thus the process continues. The destruction of the uncalcified matrix substance appears to be a steady process of solution or erosion.

In some instances the blood vessel completely destroys the matrix substance with the cells. This happens when the invading vessels are very large. Usually, however, more massive parts of the matrix framework, even though uncalcified, survive. On any framework which survives, osteoblasts settle and use it as a base for trabecular formation. This type of invasion process varies much with the degree of rickets. If the rickets is just beginning or is not severe, the invading vessels remain small. In that case, the massive parts of the framework of matrix substance quite regularly escape. It is when the disease is advanced and the invading units have become large channels that the massive parts of the framework go down with the cell capsules. The methods of invasion are exactly the same whether the vessel happens to take origin from the shaft, periosteum or cartilage.

Fig. 8—Photomicrograph (high power view) from a microscopic section of the tibia of a puppy in which rickets had been produced experimentally.

The picture is shown to illustrate the enormous dilatation of the vessels which occupy the advancing surface of the vascular bush when the latter has attained large size. The vessels were injected with india ink. The black represents the greatly dilated lumina of the vascular channels. Surrounded in front and on the two sides by the india ink is a mass of blood cells. In the path of this invading mass of blood vessels both cartilage cells and matrix substance alike are being destroyed. On the right of the central vascular bush can be seen a partition of cartilage beyond which at the extreme right is another vascular bush, only partly shown.

It does not require any great degree of imagination to picture the gross effects on the proliferative cartilage of the irregular invasion. The invading blood vessels with their accompanying cells create ever enlarging holes, which, of course, are not actual cavities since they are filled with marrow elements brought by the blood vessels and contain in addition cartilage remnants. If one imagines a bush of invading blood vessels as a cast, and the hole in the enveloping cartilage as the mold, it will become apparent that the hole is not a simple cavity but has innumerable thin, sinuous recesses, larger ones corresponding to the larger branches, into which open smaller ones corresponding to the smaller branches, into

which in turn open still smaller ones corresponding to the smallest branches. What we are attempting to do by this comparison is to make clear that the invading blood vessels through their branching penetration reduce the enveloping cartilage to innumerable partitions. The osteoblasts, which accompany the blood vessels, settle on the surfaces just as they settle under normal conditions on the surfaces of the partitions of matrix framework and cover them over with osteoid bone. These partitions are frequently composed of both matrix substance and cells. Thus in rickets trabeculae are formed in the interior of which are cartilage cells. They belong to the chondro-osteoid trabeculae already mentioned. The chondro-osteoid trabeculae form an interlacing network and twist about in every direction without any semblance of plan. The reasons are evident enough in their mode of formation and the action of mechanical forces.

Cause of the irregularity in the invasion. Why is invasion of the proliferative cartilage so irregular in rickets? The explanation that has been given general acceptance is that of Schmorl.[3] He held that the blood vessels found it easier to grow through those places where calcification in the proliferative zone of the cartilage was defective than where it was normal. Accordingly, the capillaries chose the defective spots, and after their penetration, grew into large vessels and drew away the circulation from the calcified portions. Schmorl,[3] therefore, assumed defects in calcification of the cartilage as the essential primary condition. He offered no explanation why they occurred. Given the defects, the train of events developed in a natural sequence.

Schmorl[3] based his hypothesis on the study of histological preparations which he considered to represent early rickets. The illustrative picture which accompanied his article (see Table 1 in Schmorl's article) depicts beautifully blood vessels growing through large gaps in the zone of calcification. However, it shows that the rickets is already well advanced. We are under the impression that Schmorl's hypothesis is not correct. We give our reasons later.

In the rat the circulation at the cartilage-shaft border is not withdrawn at the onset of rickets. On the contrary, the capillaries all along seem to be distended with blood. The cause of the irregularity does not seem to lie, therefore, in any local circulatory failure. In the human being, also, at the beginning of rickets the circulation at the cartilage-shaft junction does not seem irregular.

In approaching the problem it is safe to proceed on the assumption that blood vessels will break through where they can. In some instances they are obstructed. First, obstructions may be subchondral. Complexes of branching or interconnecting trabeculae may be found under the cartilage which in the plane of the histological section appear to be preventing access of the blood vessels. These are encountered particularly at the slow growing cartilage-shaft junctions. When crushing of the calcified cartilaginous framework at the extreme end of the shaft has taken place, the bent spicules or fragments may block the regular channels of advance.

Second, the obstruction may lie in the cartilage at the cartilage-shaft junction. With the development of the rachitic state the cartilage as a whole becomes resistant, as will be explained later. A general resistance does not explain local differences, but it serves to delay initial penetration and may add to the effects of other factors, for example, compression, and cause irregularities in the circulation, as is pointed out below.

Local obstruction usually takes the form of compressed cartilage which is most apt to be situated at the points of impingement of individual trabeculae or groups of trabeculae. The cartilage may be compressed to such extent that it becomes stratified. Compressed cartilage evidently may furnish considerable obstruction to vascular penetration and even slight compression, some obstruction. If the compression has produced stratification, obstruction will be very great. In several of our specimens the stratified under surface of the cartilage seemed to have formed a resistant wall. We are under the impression that even slight disarrangements of the cartilage by which the cells are thrown out of line increased the difficulty of invasion.

On reaching the under surface of the cartilage the blood vessels will penetrate at once, if no obstruction exists. If, however, they are unable to go forward, they often spread laterally as when growth of normal cartilage is suddenly arrested for any reason and in so doing destroy the spicules of calcified matrix substance on either side, thereby creating pockets. From these they attempt to break through the barrier into the cartilage. This they will do ultimately.

Third, obstruction, theoretically, may exist in the form of a very heavy deposit of lime salts in the cartilage bordering on the shaft. Obviously, if lime salt deposition has been completely suspended, there can be no obstruction from that source. If the deposition ahead of the vessel is light, the vessel will carry it away very easily. This the invading vessels

do continually. We have found instances in which the bare capillaries themselves appeared to be successfully eroding calcified cartilaginous matrix framework. If the deposition in front of the vessel is heavy, it may act as an obstruction. We have evidence, however, that the larger vessels lying just under the cartilage so alter the cartilage immediately in front of them as to prevent it from taking up calcium salts. As a consequence inhibiting barriers of lime salt deposition do not ordinarily form in front of the vessels. This subject will be discussed later.

After the vessels have passed the barrier at the cartilage-shaft junction, they are free to expand. We hesitate to say with Schmorl[3] that those which have succeeded in penetrating take away the circulation from their fellows. With their increase in size, however, they do transmit increased blood volume, whereas the vessels which fail to penetrate remain small.

At the cartilage-shaft junctions of the slower growing epiphyses the causes of the irregularity of invasion are not entirely clear. Obstruction from compression may occur, but is not usual. At those locations vascular trunks appear to reach the under surface of the cartilage only at certain places. Between these places one finds heavy trabecular formations. In other words, channels exist between the trabecular formations leading to the under surface of the cartilage and the invasion of the cartilage takes place at the points where these channels open, i.e., where the blood vessels happen to lie.

Calcified matrix framework forms the boundaries of the apertures where the vessels have penetrated. Either the vessels that penetrate or others attack this calcified material from the sides. The erosion process goes on for as long as the rickets lasts. As the result, the original small holes of penetration become larger and larger. The masses of calcified matrix substance which intervene between the points of penetration become correspondingly reduced. After the rickets has persisted for a time the large holes and the small fragments of calcified matrix between give a most misleading idea in regard to the condition at the time when the rickets began.

Why do the apparently withered branches of the cartilage canals come to life and the perichondrial vessels grow out into the cartilage? When the vessels of the shaft succeed in budding into the cartilage it is easy to understand why they should continue to grow. But why should the vessels of the cartilage canals and the perichondrial vessels

join in the invasion? The mere fact that capillaries from the end of the shaft normally grow into the proliferative cartilage makes it seem certain that the cells of the latter when fully developed must possess chemotactic properties. In cases of rickets we can often follow small arteries through the shaft and observe that on arriving in contact with the cartilage they undergo extreme dilatation. When the fully grown cartilage cells accumulate about the descending branches of the cartilage canals, they must stimulate the capillaries in the canals to growth exactly as they do the capillaries of the shaft. How it is accomplished is unknown. The situation must be similar to that when blood clot forms or dead tissue develops in the neighborhood of capillaries. As a possible reason why the budding out process does not occur under normal conditions we point to the thinness of the layer of fully developed cartilage cells and the fact that it is taken up as fast as formed by the shaft vessels.

The budding of the canals does not occur unless the disease is severe and prolonged and may not occur even then. One branch may bud and another not, or the level at which budding occurs may be different. These variations may be explicable on the basis of differences in length of the blood vessels in the descending branches.

The participation of the perichondrial vessels must be, also, in response to chemotactic influences originating in the accumulated mass of fully mature cartilage cells.

Schmidt[28] and Schmorl[29] seem to regard the invasion from the cartilage canals in rickets as not only abnormal but most injurious. We admit that it never occurs normally. It is obviously, however, an effort to compensate for the inability of the shaft vessels alone to meet the situation and as such it is most successful. When the healing process once begins, it is completed much more rapidly as the result of the previous coparticipation of the vascular system of cartilage and perichondrium in the invasion process.

Both Schmidt[28] and Schmorl[29] hold that the cartilage canals are the chief agents for conversion of cartilage in rickets. Our study of cleared bones demonstrates that such is not the case. In the great majority of instances the vessels from the shaft take the entire or else the major part of the burden. However, in the ribs and occasionally in other fast growing bones the canals dominate the picture, becoming enormous and reaching to the cartilage-shaft border. In that case the invading vessels from the shaft remain very small. Whether or not the cartilage canals

develop to large size depends, first, on the amount of accumulation of the mature proliferative cartilage and, second, the extent and effectiveness of the obstruction at the cartilage-shaft junction. When the canals become enormous, the shaft vessels have been effectually blocked for a long time.

The changes in the cartilage. We are much handicapped in studying the cartilage in the infant because of difficulties in interpretation. Standards of comparison are lacking, owing to variations in age and growth rates at the various bone ends. Also, we are not sure that the disease from which the infant died, in particular if accompanied by extreme dehydration, may not have altered the cartilage. Recently, since we have become aware of the frequency of vitamin C deficiency, we have often felt insecure lest it might have been a factor in altering the cartilage cells. Finally, in certain instances it has been difficult to exclude congenital syphilis which may affect the cartilage. Hence, we are particularly grateful to Dodds and Cameron[6] for their beautiful studies of the effects of rickets on the proliferative cartilage in the rat.

We have already mentioned that Dodds and Cameron[6] found the fully grown cell of the proliferative cartilage shorter than normal, though of the same breadth. We have thought that in some cases of human rickets the fully grown cell was smaller and more ball-like and possibly that the capsule was slightly thicker.

We now call attention to certain degenerative changes which are particularly characteristic, if the disease is at all severe.

Pseudo-osteoid transformation. We have chosen this designation because it denotes what actually transpires, namely, that the cartilage becomes changed into a form which greatly resembles the osteoid tissue produced by the osteoblasts. If we try to trace the process, it is somewhat as follows: The matrix substance becomes yellow and the large blue-staining cartilage cells and their capsules begin to lose their color. The cell capsule retains its blue stain better than the cell body and the nucleus even better than the capsule. Both cell and cell capsule shrink. The matrix substance increases in amount and the cell capsule becomes thin. Finally, the cartilage cell with its lacuna becomes reduced to the size of a bone corpuscle and in its setting in the matrix substance looks like one. There are great variations. In some cases the cartilage cells remain large. The nucleus and capsule retain the blue stain but the cell body becomes clear. Later, the capsule and still later the nucleus lose

their blue stain. The capsule seems to merge with the matrix but retains at the cell margin its refractile properties. Finally, the cell without any color looks like a ghost of itself and can be identified chiefly because of differences in refraction of its capsule. All this takes place with little shrinkage. In some instances the cells and capsules contract to very small size, retaining the while their purple color and looking like minute balls. In general, the closer to the blood vessels, the more the condition resembles osteoid and the further away the more numerous are the cells which still retain normal features (staining properties, size, etc.). There is evidently great difference, also, in rate of change. In some instances it must be abrupt, in others gradual.

Development of bizarre forms. The cartilage capsules and cells shrink and assume a globular or spheroidal form, at the same time staining so heavily with hematoxylin that the shade is a deep purple. Depending on the degree of contraction, these cells show great variations in size, from dimensions of the full sized proliferative cartilage cell to those of the bone corpuscle. Occasional cells contain dumbbell-shaped nuclei and others double nuclei, as if division had taken place. These peculiar cells are apt to be found in clusters at the tips of the peninsulae or in fringes along the sides, intermingled with other abnormal forms. Occasionally one sees them in the heart of chondro-osteoid trabeculae well down in the shaft. Ultimately, these cells lose the power of taking hematoxylin stain, become smaller and take on the appearance of bone corpuscles.

We think that these degenerative transformations of the cartilage are connected with incomplete exposure to the blood. If the exposure is fairly rapid, the transformation to the bone corpuscle-like forms is rapid. If very slow, the various intermediate forms develop. Under normal conditions the capillary is in contact for only a brief time with the capsule before penetration takes place. According to Dodds and Cameron's[6] calculations, a capillary must penetrate seven cartilage-cell capsules daily in order to meet the requirements of normal growth in the young rat. Under the irregular invasion of rickets the cartilage in various localities must remain for some time in sufficient proximity to the blood to be affected by its pH or some other factor without being actually attacked. Under those circumstances it passes over into pseudo-osteoid, with or without the production of the curious intermediate forms. We believe that the cartilage cell cannot be exposed to the influences of the blood

and remain cartilage. A change is forced. Harris,[30] Ham,[31] Wolbach[22] and others all are convinced that normally the cartilage cell is dead at the time when penetration occurs. Dodds and Cameron[6] have reported finding cartilage cells in normal bone which seemed to be excellently preserved after liberation from the capsule and we have made the same observation. We used to think that in rickets actual metaplasia took place, i.e., that the cartilage cells, having been reduced to the size and appearance of bone corpuscles, became such. Further studies, however, convinced us that they actually died. An inspection of old chondro-osteoid trabeculae will often reveal slit-like spaces empty of cells, which represent the original lacunae and can be identified only because of retention of the refractile qualities of the walls.

The chemical changes in the blood peculiar to rickets may be a determining factor. One sees degenerative changes in the cartilage in scurvy and congenital syphilis, but not just like the ones described.

It is necessary to mention other degenerative changes. In many cases of severe rickets the fully grown cells seem to be generally changed. They are very small and irregular and the matrix substance greatly increased. The columnar arrangement is poorly preserved, so that the cells as a whole have a jumbled appearance. The staining reactions to hematoxylin and eosin are preserved. In some of these cases one finds that the cartilage at the junction with the shaft is greatly compressed and we have wondered if the condition of the cells described might not be due to failure in nutritive supply. It is also possible that pressure influences may be responsible for the changes.

In the puppy suffering from rickets we have encountered actual death of the cartilage cells. The cells affected were in family groups, that is, columns of cartilage cells would be necrotic whereas neighboring columns would seem fairly normal. In the two animals studied the accumulation of the proliferative cartilage was nothing short of enormous, and the cartilage-shaft border was so compressed that one gained the impression it might have been difficultly pervious or actually impervious to the lymph.

Cartilage may become completely necrotic. It is common in the rat to find these necrotic areas at the cartilage-shaft junction. They are often hemispherical and are sharply circumscribed. One occasionally finds them in the human being in the same situations. Dodds and Cameron[6] ascribe the necrosis to the action of mechanical factors. We have found

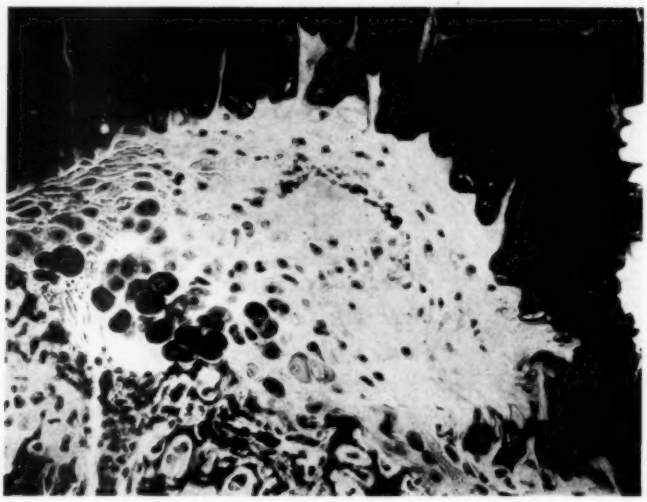

Fig. 9—Photomicrograph (high power view) from a microscopic section of the upper end of the tibia of a rat in which the rickets had reached an advanced stage of development.

The picture shows one of the areas of dead and dying cartilage cells lying just above the shaft. In the lower central and left hand regions one can see the phenomenon of rejuvenation of cartilage cells, described by Dodds and Cameron. No blood vessels are growing into the area from the shaft. However, a blood vessel, partly injected with india ink, can be seen arching across the dead area in its upper part. We are inclined to think that the occasional vessels seen in these dead areas have found entrance after the death of the tissue has occurred.

areas in which no evidence existed in the tissues themselves either of compression or tension, but we could not exclude the possibility of the intermittent action of mechanical factors and have wondered if cell death resulted from failure in nutritive supply. The necrotic areas were bounded on the shaft side by barriers through which capillaries were not penetrating. Schmorl and Lossen[26] produced such necrosis in the normal rabbit by cutting away bone immediately under the cartilage. Where granulation tissue had grown into the cavity, the overlying cartilage cells remained alive but where the cavity was filled with blood clot and debris the cartilage cells had undergone complete necrosis. In the case of the rat, one sees in some instances blood vessels traversing the necrotic

areas. We have been inclined to think, however, that they had found entrance after the necrosis had occurred. Between some of these areas of necrosis and the shaft we have found scattered cartilage cells, not only alive but apparently dividing, the rejuvenation described by Dodds and Cameron[6] (Fig. 9). We have thought that perhaps just sufficient lymph passed the barrier to keep alive these cells and caused them to undergo these curious changes.

Is the proliferative cartilage abnormally resistant? The obstruction to invasion seems to lie chiefly at the cartilage-shaft junction and to be of a mechanical nature, as already pointed out. At the extreme periphery where compression does not occur so readily and the lines of normal growth are better preserved, invasion is often deep. But conditions may be different there than in the interior on account of the proximity of the perichondrial circulation. In the human being, dog, rabbit and rat invasion may be entirely absent or poorly developed in one place but in an adjacent place approximate the normal. The fact that invasion can extend to the normal limit anywhere might be used as an argument against special resistance in the cartilage itself. However, if one remembers that growth of the proliferative cartilage is diminished or actually stopped, as Dodds and Cameron[6] showed was the case in the rat, slowly advancing vessels, if given time, would penetrate to their limit. Chemical studies have not been made on the cartilage in rickets, so far as we know, though the pH has been shown to be unchanged (Pierce[32]). Although Dodds and Cameron[6] have demonstrated that the cartilage cell is reduced in size (in the rat) and we have pointed out that the cartilage does undergo most peculiar changes, these peculiarities do not necessarily signify that the cartilage is changed chemically. The fault may lie not in the cartilage cell but in the altered chemical conditions in the blood or perhaps in the lack of the directing influence of the normal calcium deposits. Proof, however, that the proliferative cartilage is actually more resistant is afforded by treatment, for when vitamin D has produced its effect, the cartilage is rapidly penetrated and removed.

The rachitic intermediate zone (or metaphysis). The steady accumulation of proliferative cartilage and the irregular invasion and clumsy conversion of the cartilage by the blood vessels are responsible for the formation between the end of the shaft and the generating zones of the proliferative cartilage of a hodge-podge, known as the rachitic intermediate zone or, in the German literature, rachitic metaphysis. If one

will but think of it as a large mass of proliferative cartilage containing in its interior the vascular bushes which have grown into it from below and perhaps, also have entered from above and the sides, and remember how the vascular bushes bring marrow cells with them and break up the cartilage into chondro-osteoid trabeculae, the histological picture ought to be clear. The masses of proliferative cartilage which extend toward the shaft as peninsulae or ribbons or appear as islands, represent merely the remnants of the parts originally skipped in the invasion process. The blood vessels are the trunks, stems, and terminal branches of the vascular bushes, whether entering from the side of the shaft, the cartilage or perichondrium. Their bush-like formation is not apparent any more than the structure of a tree would be evident in any section in a single plane, unless it chanced to be vertical through the trunk. The chondro-osteoid trabeculae represent the partitions of the matrix framework of the cartilage, freed of cartilage cells by the blood vessels and covered by the osteoblasts with osteoid bone. Those which contain inclusions of cartilage cells represent the thicker partitions of cartilage between vascular branches on which osteoblasts have settled as if they consisted of matrix substance alone. The cells, lining the chondro-osteoid trabeculae, are osteoblasts with an occasional osteoclast. The spaces between the chondro-osteoid trabeculae are very narrow, as Dodds and Cameron[6] point out, and are filled by the blood vessels and a sparse connective tissue network. Marrow cells are represented only by stragglers. As might be expected, the chondro-osteoid trabeculae are most numerous in those parts which were invaded first, i.e., on the shaft side. The cells of the peninsulae are normal looking fully developed cartilage cells, but in the peripheral regions and especially at the tips are found the pseudo-osteoid transformations and the bizarre forms of cells which have been described. Here and there deposits of calcium salts may be found, marking focal areas where some time in the past local conditions happened to be so much more favorable than elsewhere for lime salt deposition as to confer on the areas in question a selectivity. It will be noted that many of these lie at the tips of the peninsulae of cartilage but they may occur in various places and, if healing has commenced in earnest, they often run crosswise in strata formations. Always in the rachitic metaphysis one can see the effects of the operation of mechanical forces.

Evidences of the operation of mechanical forces. In many places in the rachitic intermediate zone one can see the marks of mechanical

forces. We have already described the compression changes at the cartilage-shaft junction. The peninsulae of proliferative cartilage which extend from the main mass toward the shaft are almost always bent at some part of their course and occasionally are even doubled back. It is common to find groups of cells which have evidently been compressed or stretched. The cartilage columns at the periphery of the proliferative zone may fan at angles of 45 or even 90 degrees. The entire phenomenon of cupping is a response to mechanical influences. Cell columns at the cartilage-shaft border may be stretched apart. In the case of the costochondral junction, especially, tension becomes a most important factor and may cause the lower part of the intermediate zone to give way, so that the upper part is pulled around against the outer surface of the shaft.

Mechanical forces seem to be operating aimlessly. On the contrary, they determine the subsequent architectural arrangement. Before explaining how this comes to pass, we must record our observations on calcification of the cartilage in rickets since they supply the clues to the subject.

Observations on the calcium deposits which occur sporadically and during the course of healing in the intermediate zone. Since calcification is selective, it follows that it must be determined by two conditions, one general, the other local. The general condition is represented by some chemical equilibrium which we have symbolized by the S.P., for calcium phosphate in the blood. The local conditions determining calcification are unknown. Robison[33] has proposed phosphatase which the cartilage cells are supposed to elaborate. Shear* has suggested, as another possibility, a slight shift in the pH to the alkaline side at the calcification site. If the S.P. is high enough, calcification will occur in bone and cartilage, even if the local conditions are not especially favorable. If the S.P. is sufficiently low, calcification will not occur anywhere, irrespective of the local state. If the S.P. is at certain intermediate values, calcification will take place only if the local conditions are in some way peculiarly favorable. It is possible to postulate, therefore, that the necessary local factors are present whenever lime salts deposit selectively; also, that the sites of deposition are within the diffusion range of the lymph, since the lymph is the only source of the necessary material.

We have obtained information on the subject of calcification from

* Personal communication.

the examination of cleared specimens of rachitic bones in which the deposits of lime salts stained with alizarin show with clearness in the transparent medium of the cartilage.

Before proceeding to the results of our studies, however, it is necessary to point out that lime salts deposit in two different kinds of tissue in the rachitic intermediate zone, namely, in the chondro-osteoid trabeculae and in the proliferative cartilage. In cleared specimens one can easily distinguish the trabecular deposits from those which have occurred in the cartilage. When deposition takes place in the chondro-osteoid trabeculae, the pattern seen is coarse and plainly that of trabeculae, whereas when the deposits occur in the proliferative cartilage, the pattern is fine and regular, evidently that of the matrix framework. It is interesting that in some cases calcification of the chondro-osteoid trabeculae precedes calcification of the cartilage. It is common, however, to find calcification occurring focally at the same time in both tissues. Our present observations are limited to the study of lime salt depositions in the cartilage.

Müller[34] first called attention to the fact that, when rickets healed, calcification took place in a stratum of the proliferative cartilage which was situated at some distance from the end of the shaft. The lime salts skipped the cartilage adjacent to the end of the shaft and chose cartilage at some distance beyond. Müller[34] further recognized that the stratum selected corresponded in its situation to the so-called provisional zone of calcification, i.e., the zone in which deposition would have occurred if rickets had never supervened. He also commented that the cartilage chosen must be chemically different from the rest. When we examine cleared specimens of rachitic bones, especially if treatment was commenced a few weeks before death, we often find the stratum of lime salt deposition described by Müller (Fig. 10, *a*). It is always separated from the end of the shaft by transparent cartilage, the thickness of which varies with the length of the intermediate zone. We find that it represents, relatively speaking, a smooth surface on the upper side but an irregular surface on the lower (shaft side). Obviously, on the upper side there is a smooth limiting surface of some kind. We observe, also, that the stratum of lime salts extends higher and is hence thicker at the extreme periphery than elsewhere and also that it does not reach the perichondrial membrane but is separated from the latter by a layer of transparent cartilage. The surface which it presents toward

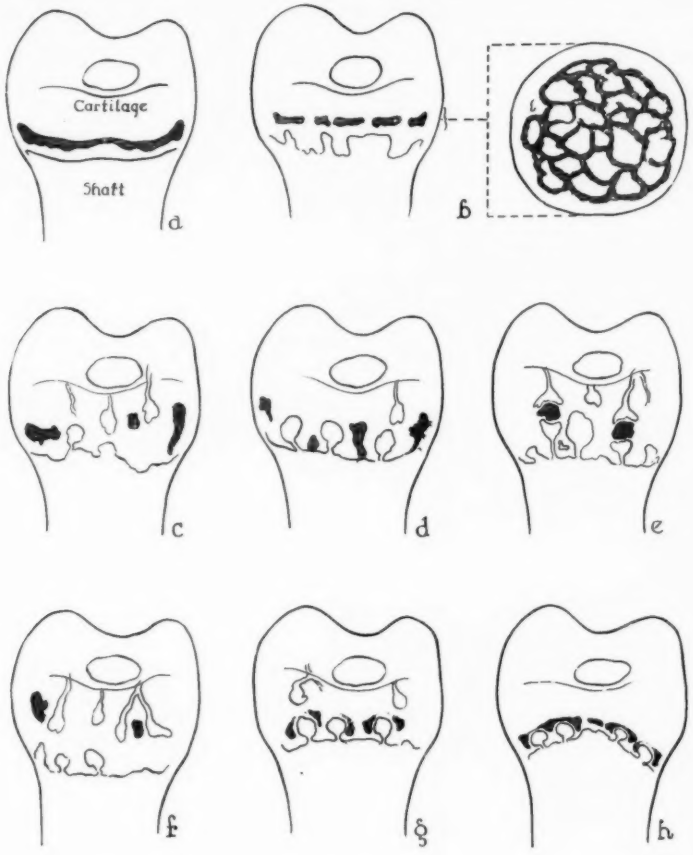

Fig. 10—Diagrammatic drawings in single planes, showing relationships of lime salt depositions in cleared specimens.

a. Stratum of lime salt deposition in substance of proliferative cartilage. The distribution is zonal.

b. Deposits of lime salts in zonal arrangement. In reality, the stratum of lime salt deposition is full of defective areas caused by the inhibitory influences of the blood vessels. The circular drawing to the right, showing the stratum on end, makes clear why the deposit seems fragmentary in single plane preparations.

c. A lime salt deposit paralleling perichondrial membrane.

d. Lime salt deposits between vascular bushes growing out of the end of the shaft.

e. Lime salt deposits between vascular bushes growing out of the end of the shaft and the descending branches from the cartilage canals.

f. A lime salt deposit between descending branches of cartilage canals and one between descending branch of cartilage canal and perichondrial membrane.

g and *h.* Dome formation over vascular bushes partial, and complete.

For a complete understanding of the drawings the reader must consult the text.

the perichondrial membrane is smooth and parallel to the latter. Such strata of lime salt deposits in the substance of the cartilage are rarely complete, and are only so when the rickets is comparatively early and invasion has not developed to any extent. If the invasion from the shaft has reached the point at which the blood vessels come close to, or extend into or actually pass through the stratum, we find that the latter is defective and that the defective areas are circular and correspond to the location of the vessels. In other words, where the vessels ascend from the shaft, lime salt deposition has not taken place, but it has taken place between. When under such circumstances we examine the stratum of lime salt deposition from above, we find that it is filled with crater-like holes (Fig. 10, *b*) and that in the hole or just below or protruding above are bushes of blood vessels. The same conditions hold true in case of the descending branches from the cartilage canals. Where the latter approach the stratum of lime salt deposits from above or actually pass through, circular apertures exist. When the stratum shows this perforate condition in the cleared specimens, the deposits appear in the histological sections as fragments which, however, are in line with each other in a zonal curve.

Calcium deposits may also form parallel to the perichondrial membrane (Fig. 10, *c*). In that case they do not touch the perichondrial membrane but are separated from it by a clear layer of cartilage cells. The surface which presents toward the perichondrium is smooth. Obviously, there must be some smooth surface of limitation on the perichondrial side which prevents the spread of calcification in that direction. We have observed in the case of the puppy having rickets that the pattern of the deposits corresponded to the pattern of the vascular network of the perichondrium, but we were unable to determine the exact relationships.

Depositions of lime salts in the cartilage also occur in definite relationship to the blood vessels growing into it from the end of the shaft, the perichondrium or the cartilage canals. The favorite situation is between blood vessels (Fig. 10, *d*). Thus, it is common to find deposits between vascular bushes emerging from the end of the shaft or between a vascular bush and perichondrial vessels. If cartilage canals play an important part in the invasion, one may find them lying between a vascular bush growing out of the end of the shaft and a descending branch of a cartilage canal (Fig. 10, *e*). Occasionally one finds

them between two descending branches of cartilage canals or between the latter and perichondrial vessels (Fig. 10, *f*). When lime salt deposits occur in relationship to the blood vessels growing into the cartilage, they are separated from the latter by a zone of clear cartilage. Moreover, if the vascular bush presents an even rounded contour, the surface of the lime salt deposit facing the bush is correspondingly concave and smooth, paralleling the surface of the bush. Most commonly the deposits of lime salts lie opposite the middle level of the bushes. Quite often, however, they are continuous with the shaft. In that case, the appearance is that of promontories or pillars of calcified material rising out of the top of the shaft between the vascular bushes (Fig. 10, *d*). If lime salt deposits exist between the vascular bushes and the perichondrial membranes, it is quite common for them at one point or another to join lime salt deposits in the perichondrial membrane by means of an arm or arms. In that event it can sometimes be demonstrated that vessels extend from the perichondrium into the substance of the cartilage above and below the extending arm, separated by clear cartilage. Occasionally we encounter lime salt deposits lying off an isolated vascular bush (Fig. 10, *g*). Thus, two vascular bushes are not essential for the production of lime salt deposits in the cartilage. Moreover, we have found instances in which the lime salt deposits, thick at the sides of the bush, extended as if to surmount the entire bush. However, as the summit was approached, the lime salt deposition became thinner and over the top stopped altogether (Fig. 10, *h*). In one instance, we have found lime salt deposits, which were thick between bushes, extending completely over the summits, forming domes. However, the tops of the domes were much thinner than the rest and in some instances were incomplete. In this instance and in other instances in which domes had started to form, the proliferative cartilage was relatively short (femur). The impression was obtained that the uppermost lime salt deposits were close to or actually in the top of the zone of large cartilage cells where zonal deposition of lime salts occurs; in other words, that the calcification might be a combination of perivascular and zonal deposits. We have not seen any indication of dome formation over the vascular bushes when the proliferative cartilage was exceedingly deep, as in the case of the ribs.

It is difficult to think of a single hypothesis which explains the location of these focal depositions of lime salts in the rachitic intermediate zone. One factor is certain, namely, the lymph, for the only source of

lime salts is the lymph, as already stated. When deposits lie between vascular bushes, the source of the lymph must be from the bushes themselves. When the lime salts deposit in stratum formation across the cartilage, the source of the lymph is presumably from the end of the shaft. At least, in a single experiment reported by Schmorl and Lossen[26] lime salt deposition occurred in stratum formation in the cartilage above the points where circulation in the shaft had been preserved but failed to occur above the points where it had been blocked by dead tissue. Another factor may be continuity. We have gained the impression that lime salt deposition occurring at a given focus may extend from that focus by continuity. One reason for thinking this is that lime salt deposition, when rickets heals, often tends to extend in processes which become more tenuous until they stop altogether. Formerly, we explained stratum formation on the hypothesis of ageing of the cartilage cells. We thought that, when the cartilage cell developed to a certain maturity, it generated the local factors necessary for lime salt deposition but, if deposition did not ensue, they were lost. It is impossible, however, to explain the sheets of lime salt deposit which parallel the perichondrial membrane or the deposits which form around the vascular bushes on the ground of ageing of the cartilage cell. The formation of these deposits must depend on circulatory conditions. The tendency for calcification to take place in the cartilage intervening between blood vessels suggests that a predisposing factor may be lymph stasis. We are inclined to think that the deposition around blood vessels is determined by the diffusion of the lymph. If the lymph flow is sufficiently brisk, so that some essential factors, such as oxygen tension, are maintained, lime salt deposition is inhibited, i.e., phosphatase is destroyed or the pH optimal for the selective deposition of lime salts, is prevented from developing. If, however, the lymph flow is sufficiently diminished, the conditions favorable for lime salt deposition become fulfilled. In order to explain the absence of the formation of lime salts above the vascular bushes growing out of the end of the shaft, or below the descending branches of the cartilage canals, according to this hypothesis, it is necessary to think that the diffusion of lymph takes place much more readily along the vertical lines of the cartilage, i.e., up and down in the direction of its columns of cells and of the matrix framework than across them. It is possible that the same necessary local conditions may be caused to develop in two totally different ways. It seems difficult to explain the zonal distribution of lime salts

on circulatory grounds alone. If, however, further studies should prove that anatomical conditions favored lymph stasis in the stratum of cartilage immediately underlying the generating zones, the single hypothesis of variations in the lymph flow would suffice. In any case, the observations that lime salt deposits tend to develop in the cartilage at the sides of and especially between blood vessels and tend to avoid the pathways of vertical growth is of great practical importance, because it offers an explanation for the variations in calcification at the cartilage-shaft junction in rickets. Under the conditions of rickets the cartilage in front of the dilated blood vessels is prevented from developing its selective power to take lime salts out of the blood. We believe, therefore, that the generally accepted hypothesis of Schmorl[3] to explain the irregular invasion which occurs in rickets is wrong. The mere fact that lime salt deposition fails in the pathways of the descending branches of the cartilage canals is by itself sufficient to destroy Schmorl's[3] hypothesis, because the descending branches come from widely separated fixed points and occupy fixed lines in the cartilage and have no ability to conform in their growth to pre-existing holes in the zone of calcification. Schmorl[3] put the cart before the horse.

Our observations of the relationship of the lime salt deposits to the vascular bushes, which represent large vascular complexes, are perfectly clear. No doubt whatsoever exists that the large vessels inhibit the deposition of lime salts from occurring along their paths of growth. When the invading units are of very small size, the cleared specimen technique is too coarse to reveal relationships. We believe, however, that the principle that the blood vessels under the conditions of rickets inhibit lime salt deposition in their pathways is the cause of the irregular deposition of lime salts at the cartilage-shaft junction from the very beginning. The minute defects in calcification are to be referred to minute variations in the circulation in the shaft immediately beneath. As the variations in the circulation at the end of the shaft become greater, the corresponding defects in calcification become greater, until the phenomenon becomes so well defined as to be obvious in the cleared preparation.

We should like to add in conclusion that the relationships between lime salt depositions in the cartilage and the circulation are not apparent in the single plane of histological preparations. Visualization in three dimensions is essential.

How mechanical forces actually determine the architectural arrange-

ment of the intermediate zone. The epiphyseal cartilage, transmitting its superimposed weight, rests on the trabecular framework. Not all the trabeculae function equally as supporting piers. Some groups act as main supports, others minor or secondary supports. These latter, presumably, are destined soon to be removed. The compression of the cartilage is greatest, naturally over the parts of the trabecular framework which function as major supports. The vessels penetrate the cartilage where it is least compressed or not compressed at all. It follows that they enter between the major points of support. It is a noteworthy and most important fact that, as just explained, when lime salts fall, they avoid the cartilage in front of the vessels and choose the cartilage of the sides, i.e., in front of the main supporting piers. Because the matrix framework of the cartilage in front of the supporting piers has been compressed, the lime salt deposits are of an extremely dense character. The parts of the proliferative cartilage which remain untouched by the invading vessels and hence persist as peninsulae are those which have been protected by the compression barriers. It, therefore, comes to pass that the supporting piers, the deposits of lime salts and the peninsulae of proliferative cartilage are in line with each other. The architectural arrangement, then, which develops as the disease extends, is this: The weight-bearing complexes comprising trabecular piers, calcified matrix formations, and peninsulae of proliferative cartilage alternate with the invasion complexes of superfluous parts of the trabecular framework, vascular bushes with their cellular components and the lime salt free areas. Since the weight-bearing lines in the bones pass through the peninsulae, it is small wonder that these masses of cartilage in particular show the effects of pressure (Fig. 11).

The architectural arrangement in chronic rickets. In chronic rickets lime salts keep depositing but only in certain places. The areas free from lime salt deposition lie at the invasion sites. The deposits are situated between them. They seem particularly dense. The extreme density is due to two factors, first compression and second, slow growth. Compression, by flattening the lacunae, collapses the framework, so that, when it becomes permeated with lime salts, the deposition is condensed. Slow growth, which is certainly very common in, if not a regular feature of, chronic rickets, results in an extension of the calcification into the cross and minor longitudinal partitions. Granted that in rickets a modicum of lime salt deposition continues, the alternation of lime salt free invasion

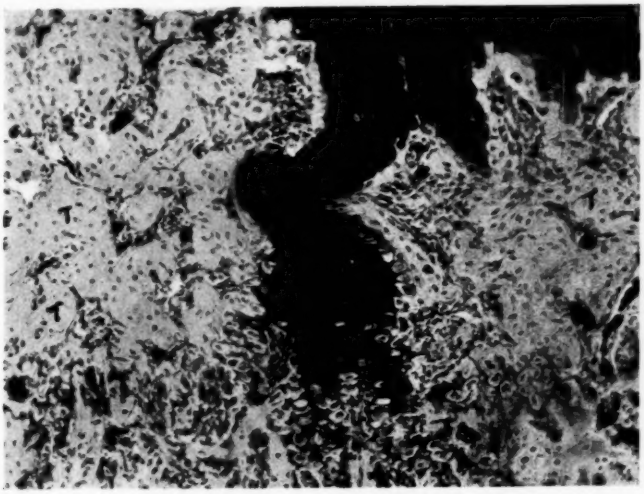

Fig. 11—Photomicrograph (low power view) from a microscopic section of the upper end of the tibia of a rat.
The picture shows beautifully the effect of pressure on a peninsula of proliferative cartilage extending from the main mass towards the shaft. In some instances compression may be so great that a peninsula is actually bent back on itself. The picture also shows beautifully the chondro-osteoid trabeculae (*T*). These soft trabeculae have probably been compressed and bent to the same extent as the peninsula of proliferative cartilage. But there is no means of knowing what their original architectural arrangement was. At the tip end of the peninsula a fragmentary deposit of lime salts is present. The peninsulae of proliferative cartilage almost always show such deposits at their tips.

areas and intervening heavy deposits of lime salts in deformed and compressed cartilaginous matrix framework is exactly what would be anticipated from the principles laid down in the foregoing discussions (Fig. 12).

Does the defective deposition of lime salts explain all the pathological changes? Schmorl[3] held that every pathological change in the cartilage and bone was due to lack of lime salt deposits, and Dodds and Cameron[6] have championed this view. The argument is as follows: The lime salts, while attacking the proliferative cartilage, keep the capillaries confined in metallic tubes and force them to limit their activities to the single columns or fascicular groups lying ahead of them. When lime salts cease

Fig. 12—Photomicrograph (high power view) from a microscopic section of the upper end of the tibia of a rat.

The rickets has assumed a chronic form. The circulation was injected at the time of death with india ink. It will be observed that invasion areas alternate with areas of dense lime salt deposit. The dense lime salt deposits lie in greatly deformed and crushed formations of matrix framework. The reasons for this will be found in the text.

to deposit, the capillaries destroy the matrix walls as well as the lacunae and, therefore, no longer remain confined. Their liberation allows freedom of growth, so that individual vessels reach great size, and causes the substitution of the *en masse* for the normal invasion. *En masse* invasion is inefficient, since it involves destruction of the uncalcified matrix framework together with the cells and the framework offers more resistance than the cell partitions alone.

Undoubtedly the failure in lime salt deposition explains the changes which transpire in the shaft, the irregularity of the invasion of the cartilage, the large size of the invading vessels and the *en masse* invasion. But does it explain the increased resistance of the cartilage? When one investigates, in order to learn if the uncalcified matrix framework is serving as an obstacle, one occasionally finds a capillary traversing it as if by preference. However, in the main, even in severe rickets, the

invasion paths seem to be preferentially along the cells. Matrix substance, when calcified, obviously constitutes an obstacle, for it is common to find a spicule projecting and holding back a capillary which has already caused the cartilage on either side to give way. In the *en masse* invasion we do not find such exposed ends of uncalcified matrix framework protruding along the invasion surface. On the contrary, the framework seems to be destroyed with the cells and in occasional places even in advance of them. The framework, when uncalcified, offers little greater resistance than the cell capsules. But there is a reason for thinking that it does offer a little greater resistance, since the more massive parts of it tend to survive the attack of the vessels. The increased resistance of the cartilage may, therefore, be explicable on the "mechanical" hypothesis.

There are some reasons, however, for attributing the increased resistance, in part at least, to altered chemical conditions which prevent the matrix substance when in contact with the capillary from undergoing normal solution. For example, if the "mechanical" theory were the entire explanation, we should expect that the vessels would pass more easily where calcification exists than where it is defective. But the vessels pass through the defective areas. We are under the impression that, following treatment with vitamin D, the advance of the vessels is accelerated through those parts of the cartilage which previously had happened to become calcified as well as through the completely uncalcified portions. The peculiar slow degenerative changes and such phenomena as the "rejuvenation of the cartilage cells," described by Dodds and Cameron[6], seem more easily explicable on the hypothesis of a chemical disturbance than on a solely mechanical one.

When lime salts deposit in healing rickets, the defect in the blood has already been rectified. The two phenomena, the restoration of a normal calcium-phosphorus equilibrium in the blood and lime salt deposition in the bone and cartilage, are indissolubly united in a cause and effect relationship. If one could produce calcification without altering the rachitic condition in the blood, in other words, if one could dissociate the two conditions, the determination which was the essential factor would be most simple. It is necessary to conclude that the mechanical hypothesis *is capable* of explaining the increased resistance of the cartilage and that the circumstantial evidence in favor of the chemical hypothesis is as yet too slight to establish its validity.

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THE THERAPEUTIC USE OF VITAMIN C*

GILBERT DALLDORF

THE therapeutic use of vitamin C means to me the treatment of scurvy for I know of no important uses of the vitamin other than the prevention of what are scorbutic manifestations. The relationship between the vitamin and scurvy is extremely intimate. The presence of the vitamin in the body tissues is simply the antithesis of scurvy. The action appears to be direct and certain phenomena of scurvy have even been observed *in vitro*.

In the past, scurvy was studied when it was prevalent, but our current interest in it is not due to its prevalence but to the stimulating work of the chemists in recognizing and identifying vitamin C. This has improved our methods of studying scurvy and influenced our conception of it. All of these things may best be reviewed by a brief chronological résumé of the past twelve years. If my review is too personal a record of events in which I have played a wholly unimportant part, please forgive me. An army of workers has tramped these roads and only a few have become familiar to me. Moreover I have seen all of the developments in the light of my own experience.

Our knowledge of scurvy was considerable before vitamins were discovered. Indeed scurvy was the first deficiency disease to be recognized as such. This happened one hundred and fifty years ago. It was experimentally produced and studied thirty-two years ago and was at that time the best understood of all the deficiency diseases.

So matters stood a dozen years ago. At that time Wolbach and Howe[1] published their beautiful anatomical studies of the experimental disease and shortly afterward a large, steady supply of scorbutic guinea pigs became available to me from the biochemical laboratories of Teachers College. There, as in many another laboratory, various foods were being assayed for vitamin content by feeding experiments. In the case of vitamin C the Sherman-LaMer technique was almost universally used. This consisted of feeding young pigs graded amounts of the vitamin during a test period of three months and diagnosing the effect by a gross examination of the animals. Fragility of the jaw, painful extremities, hemorrhages

*Read February 2, 1939 at the Stated Meeting of The New York Academy of Medicine.

in the muscles and the weight curve were the criteria used. It is interesting to recall that all of the important advances in the art of canning, so far as they relate to vitamin C, were gained through countless laborious experiments of this kind. Patient assistants went from cage to cage and tier to tier pipetting measured amounts of food stuffs into the mouths of reluctant guinea pigs.

Even at that time the most active searcher for the vitamin, Sylvester Soloman Zilva,[2] had observed that fresh fruit juices bleach indophenol. Only an unfortunate error, based largely on the wish to be as precise as possible, prevented him from recognizing that the reducing power of fruit juices, as measured by indophenol titrations, is due to vitamin C. However, the feeling seemed general in most laboratories that vitamin C would never be isolated because of its instability. Zilva's courage in undertaking a most unpromising line of research was widely acknowledged.

Zilva's observation of the indophenol reaction led to a chain of events which resulted in the isolation of vitamin C. In Frankfurt, Tillmans and Hirsch[3] adopted the indophenol method as a means of controlling the quality of fruit juices being sold in their city, a matter in which the civil authorities were interested. They discovered that only fresh juices gave the reaction Zilva described, not stale juice nor artificial juice. Tillmans suspected the significance of these results at once. Zilva had observed that when decitrated lemon juice was first oxidized with indophenol it remained potent, but that on standing it lost its antiscorbutic effect. He thought that the indicator was decolorized by a substance closely associated with the vitamin which tended to prevent its oxidation. Tillmans suggested the correct explanation; namely, that the oxidation was reversible and that the first stage of oxidation left the vitamin more prone to further oxidation than when in its original, reduced form.

Szent-Györgyi[4] had, the year following Zilva's study of the indophenol reaction, isolated a reducing substance from adrenal cortex and suggested its identity with the reducing substance described by Zilva in lemon juice. Within a few years the many similarities and the distribution of these substances became clear and Szent-Györgyi and associates in Cambridge and Waugh and King[5] in this country completed the chemical studies leading to our present knowledge of the vitamin. Thus occurred what we may consider to be the important contribution of our time to the story of scurvy.

During these years I was examining the tissues of guinea pigs and learning to recognize the scorbutic process. The material immediately suggested a rather interesting line of thought, for since the animals were as uniform as possible to begin with and all had been on the experimental diets for an equal number of weeks, they were naturally most suited to a study of the effect of various degrees of deficiency. This I endeavored to do and quickly discovered that I was able to recognize distinct anatomical effects of deficiencies which were never recognized clinically, even by individuals with long experience with the experimental disease. In other words, amounts of vitamin believed to be adequate for guinea pigs actually resulted in microscopic changes characteristic of scurvy. The amount of vitamin believed to be adequate for the prevention of scurvy had to be doubled to prevent certain skeletal lesions. From Sweden, Axel Höjer,[6] at about this time, called attention to the sensitivity of the lesions in the teeth and demonstrated how they might be used in improving the biological assay methods and in shortening the test period. Because few biological chemists were prepared to make histological examinations, Celia Zall and I[7] developed a method whereby the rate of growth of the incisors of the animals could be measured and the growth rate used as a criterion of the degree of protection against scurvy. This proved still more sensitive to the effects of subclinical scurvy and showed that approximately three times the accepted protective amount was necessary to give maximum growth.

All of these methods were rendered obsolete before anything further was done with them by the chemical studies already mentioned and the wide adoption of the indophenol method for assaying vitamin C sources, a method which accomplishes in several minutes what previously had required three months. But to me the experience had served as a very impressive demonstration of the wide difference between clinical freedom from scurvy and optimal vitamin C nutrition. Many others reached the same position from different roads so that the growth of this idea occurred very quickly.

Our immediate impulse was to test the theory in man, and in many postmortem examinations since then I have searched for manifestations of scurvy. It was therefore not surprising to me when several years ago Park[8] reported a surprisingly high incidence of both radiographic and anatomic evidence of scurvy in 125 children studied thoroughly with scurvy and rickets in mind. Scurvy may be found, both clinically and

anatomically, if the search be thorough—evidence, no doubt, that many of our people still live on the borderline of vitamin C deficiency. But the search went on for clinical criteria of this mild form of scurvy. The progress of these studies in the years immediately preceding the discovery of the vitamin was based on studies of the capillaries. The capillary resistance test was first tried on scorbutic guinea pigs and later applied to apparently healthy individuals. This showed that the incidence of capillary fragility was surprisingly high, approximately 30 per cent among certain groups.

The capillary test, especially as performed with a tourniquet, is of course familiar to all of you. Hess,[9] years before my own experience, had used it to advantage in studying what he called latent scurvy and more than a generation earlier rather similar observations were made by Auspitz[10] while cupping patients.

Everyone who has used the test has learned to regret its variability and inconstancy and to deprecate its diagnostic value. Hess, however, found it distinctly positive in most cases of scurvy and we believed the average value in large groups of individuals might be still more reliable. Thus we hoped to learn about the adequacy of the vitamin C intake of different economic groups. It was also evident that capillary fragility was diagnostic if a prompt response followed specific therapy. Furthermore it was generally agreed and had been the experience of many generations of medical men that the hemorrhagic diathesis was the most characteristic manifestation of scurvy. We might expect capillary changes to be the first and most delicate manifestation of scurvy, so there existed some tantalizing reasons for treating the capillary test seriously. At any rate, many studies were made with it which showed a large part of the general population to have fragile capillaries with a rough agreement between vitamin C intake and the level of the resistance. In my own laboratories these results were supported by feeding experiments in which extracts of human tissues from the postmortem room were assayed biologically and vitamin deficiency demonstrated to be common in this way.

But soon the chemical methods were introduced and displaced the capillary test. Interestingly enough, they have also shown approximately the same incidence of partial starvation of vitamin C as the capillary tests did but the proponents of one test seldom find individual agreement between the two techniques.

The weakness of the chemical method has been that it does not of

TABLE I

CHEMICAL AND CLINICAL TESTS FOR SCURVY

	Fasting Blood (Mgs. per cent)	*Capillary Resistance. (Cm.Hg. neg. pressure)*	*Urinary Excretion following a test dose (Mgs.)*
Normals	0.80	45	44.0
Subclinical Scurvy	0.36	29	24.0
Severe Scurvy	0.064	5	2.0
Peptic Ulcer with Hemorrhage	0.33	11	8.0
Nonscorbutic Hemorrhagic Diseases	1.27	22	58.0

(With the exception of the case of severe scurvy the values are given as the averages for small groups of patients.)

itself demonstrate at what level of saturation or blood concentration of vitamin, deleterious effects occur. There have, it is true, been a few observations of associated gingivitis, but little of much weight. Most of these studies have been made by biological chemists with poor facilities for clinical observation.

Sloan and I[11] studied cases of manifest scurvy, mild or doubtful scurvy and normal individuals by all of the suggested methods including the capillary test. It was found that the fasting blood level, of all the single, simple procedures, furnishes the best evidence of vitamin C nutrition. Only the blood curve following a test dose is more precise. The total urinary excretion during twenty-four hours is frequently misleading although the excretion curve during the six hours following a test dose and even the total excreted vitamin during that period are fairly reliable. It was also found that the capillary test was as a rule positive in those individuals showing partial saturation. I have summarized the results from what we considered the best tests in Table I.

In general they conform with the experience of others. Several things may be learned from them. The fasting blood level clearly mirrors the condition of these individuals and nicely distinguishes between the frank scorbutic, the subclinical scorbutic and the normal. The capillary resistance test does likewise but is misleading in two groups. In the cases with ulcer, two-thirds of the patients gave false negative results, presumably because they were so exsanguinated that their superficial vessels were empty of blood, and rupture, if it did occur, could not be recognized.

The nonscorbutic group of hemorrhagic diseases, including a case of thrombocytopenic purpura, gave false positive results. In the first group, once relief was afforded the anemia, more revealing capillary tests were secured and these improved under vitamin treatment. In the second group no change followed treatment.

The table seems to me to serve two purposes. In the first place, the definite association of capillary fragility with degrees of unsaturation believed to be abnormal, constitutes definite objective evidence that the condition of subclinical scurvy has at least one morbid manifestation. This can be correlated with the observations already mentioned to constitute a continuous chain of evidence indicating that such degrees of deficiency are actually degrees of scurvy and not within the normal range. But much more will be required to be certain of this most fundamental point. The second use of the table is that it illustrates the methods by which vitamin C absorption, storage and excretion may be studied.

Nutrition is properly a major concern of our public health services. But there is a field of pathological deficiency in nutrition which is wholly within the practice of clinical medicine. Thus you may recall in the first of my tables the low blood concentration of vitamin C and the low urinary excretion of a small group of cases of peptic ulcer complicated by massive hemorrhages. Table II contains other information on one of these patients. You will note that, coincidental with saturation, the bleeding stopped. We have seen various cases of this kind and most of these proved to be deficient in vitamin C. This is representative of the applications we can make of our newly acquired knowledge.

There are various other similar conditions. Almost all of these seem related to known facts concerning scurvy. For example, the healing of surgical wounds may be hindered by vitamin C depletion. There is no doubt that this does occur experimentally. The issue at present is solely whether a sufficient degree of deficiency occurs in our surgical clinics to prevent union. Several writers have found cases which suggest this. The product of fibroblasts, collagen, does not form in the absence of vitamin C either *in vivo* or *in vitro*. Therefore any condition in which defective scar tissue occurs might well be held suspect, just as idiopathic hemorrhage should suggest scurvy. The laboratory can supply evidence of value, as I have shown, and the therapeutic test is usually conclusive.

Various such peculiar manifestations of scurvy are secondary in nature. Thus the ulcer patient may be presumed to have faulty absorption

TABLE II

USE OF VITAMIN C IN A CASE OF PEPTIC ULCER WITH HEMORRHAGE

Day	*Urinary Output in Vitamin C		Vitamin C Intake (mgs.)	Blood vitamin (mgs. %)	Blood in stool	Blood	
	in 6 hrs. (mgs.)	in 24 hrs. (mgs.)				Hg b. (%)	RBC (mil.)
1					4+	32	0.97
2						33	2.4
5					4+	52	
13					4+	53	3.0
22	18 (4%)	11	1000				
23	30 (6%)	54	500				
24	52 (10%)	65	500		1+		
25	134 (27%)	125	500	0.50		65	3.8
26	210 (40%)	156	500				
27	201 (40%)	202	500				
28	238 (48%)	225	500	1.05	2+	69	4.0
31-35			oral		—		
75	698 (70%)	702	1000	1.10	—		
92			oral	0.95	—		
115			oral	1.07	—		

(The lower values of excreted vitamin C in the twenty-four hour period represent losses incidental to storage overnight.)

although some are probably depleted by too restricted diets. The presence of a serious disease in no way minimizes the requirement, the insistent requirement, for the vitamins. Thus infectious diseases increase the requirements. Factors such as activity and physical exertion are important. This is by no means a new observation. The old sailing captains complained that their best, most energetic seamen were the first to be incapacitated by the scurvy, the loafers suffered last.

These are but a few of the possibilities which must be explored in explaining the unexpected cases of vitamin C deficiency. The rule we have followed has been to suspect deficiency in all cases of hemorrhage and musculo-skeletal weakness. All such patients are tested. A number

* Urinary output expressed in mgs. and percentage of intake.

are found who seem to be truly depleted and who benefit from specific treatment.

Finally, a few words concerning treatment. The vitamin may be given in the crystalline form, as tablets, or intravenously. It may be given in food. There are occasions when each method has advantages. The severe scorbutic deserves large doses of the pure substance as well as a model diet. This is true because severe scurvy is a dangerous condition, the depletion is severe and the equivalent of two or three liters of orange juice may be given in a single 10 cc. dose of crystalline vitamin C. Similarly the patient with severe hemorrhage should be given one or two large doses. A large dose is 500 or 1000 mgs. We have used 1000 mgs. as a rule but I believe that 500 mgs. is probably sufficient. Indeed it may be that 100 mgs. will accomplish as much; I do not know. Since the vitamin is nontoxic we have inclined to give large doses. We have never seen a reaction to such dosage. Our practice is to give a gram or a half gram daily.

In the mild scorbutic the vitamin is administered parenterally, if the case suggests faulty absorption or abnormal requirements, and as part of the therapeutic trial, always an illuminating matter. The treatment otherwise is dietary. The prescription of vitamin tablets would seem to have a very limited usefulness.

The use of vitamin C in pills containing all of the known vitamins and as a prolonged substitute for a correct diet appears to be a serious mistake. In the first place the stability of the vitamin in natural sources is infinitely greater than in the pure form. Twenty-five years ago Funk remarked on the stability of vitamin C in lemon juice where it withstands heating to 110 degrees. Buffers present in fruit juices are protective probably within the man as well as outside him. In the second place, the natural sources contain other vitamins, minerals and probably many wholly unrecognized factors of advantage. Thus several careful workers have demonstrated that supposedly pure but extracted vitamin C had attributes not present in the synthetic preparations. We have yet to recognize all of the vitamins if indeed we ever shall be able. The shotgun vitamin pill is therefore not a substitute for a proper diet. It is also unsound because those individuals able to afford such treatment usually do not need it while those who might be benefited are unable to buy it. A dollar will buy more vitamins in the market than in the drug store.

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THE USE OF TETANUS TOXOID IN PRIVATE PRACTICE*

ROBERT PAGE ROGERS

IT was a very logical step after the development and successful use of diphtheria toxoid to attempt similar work with tetanus toxoid. Let us first review some of the important steps by which this present knowledge has been reached. We owe a great deal of the progress to Ramon[1] and his co-workers at the Pasteur Institute. Attempts were made by others even earlier. Eissler and Loewenstein in 1915 used a formalized toxin with no success. Valle and Bazy employed toxin treated with Gram's iodine solution. Two out of seven cases had some specific antitoxin created thereby. Ramon,[1,2] stimulated by his brilliant work with diphtheria toxoid, prepared a formalized tetanus toxoid which he gave in three doses: 1 cc., 1.5 cc., and 2 cc. at three week intervals. He obtained an immunity in his series, measured by blood neutralizing tests, of from 1,000 to 3,000 lethal doses, i.e., one to three units. One cc. of blood will protect a guinea pig against 1,000 to 3,000 lethal doses. A fact of very great significance which he discovered is that the acquired reactivity persists, so that a later dose rapidly raises the titre.

In 1933 he[3] reported thirteen cases which had received on an average of three injections in 1927-28. These titrations were made in 1931-32, i.e., about four years after the immunizations. One cc. of serum protected against from 4 to 300 lethal doses, the average being around 60 or about 1/20 unit. Ramon[4] further reported in 1937 two individuals, one immunized eight years before, the other nine years previously, possessing 1/200 units titre, which he believes sufficient for protection. In eight days after the boosting dose one of these individual's serum rose to more than one unit.

It is now a law in France that antitetanus immunization is to be given to all soldiers. In 1936 over 400,000 were vaccinated. A boosting dose is to be given every five years. They are using the formalized preparation.

* Read April 13, 1939 at The New York Academy of Medicine before the Section of Pediatrics.

Reactions have been very slight. The immunity appears significantly after the second dose.

At this point, the work of these French scientists on the use of combined vaccination should be considered. In testing the titre of horse serum in horses that he was immunizing, Ramon[5] noted that the serum of some horses seemed to have a spontaneous increase in titre. On closer examination he found that these horses had abscesses or inflammation at the site of injection. The use of some foreign material injected along with the immunizing dose suggested itself. He first tried tapioca and found that this raised the resulting titre considerably. Then he tried associated vaccinations with similar results. Sacquepée and Jude[6] found that in a small series one month after the third dose of combined diphtheria, typhoid and antitetanus injection, 98 per cent had more than 1/30 unit.

In this country Jones and Moss,[7] and Cooke[8] have written concerning the use of combined toxoids. The routine procedure at the St. Louis Children's Hospital and Washington University Children's Clinic is now two injections, two months apart.

To return to a consideration of the plain tetanus toxoid, in this country Lincoln and Greenwald[9] made observations on nineteen patients who were given three doses of tetanus toxoid (formaldehyde) at weekly intervals. They had no general reactions and only slight soreness locally. One child developed no immunity, the others developed appreciable amounts. Bergey and Etris[10] demonstrated that the alum precipitated toxoid gave a level higher than one immunizing dose of 1,500 units of antitoxin. Since then Sneath and Kerslake,[11] Jones and Moss,[7] Boyd,[12] Hall,[13] Gold[14] and others have confirmed this work of Bergey and Etris.[10] A comparison of the results obtained by different workers is shown in Chart I.

Let us now consolidate and evaluate this knowledge and determine to what conclusions it leads us. First of all, what is the minimum protective blood level? From several sources we know that after 1,500 units of antitoxin the blood level rises to between 0.1 unit and 0.25 units within twenty-four hours to forty-eight hours and remains about that level gradually falling so that at the end of two weeks there is practically no protection. Sneath[15] showed that when guinea pigs were injected with a mixture of tetanus spores and 50 per cent calcium chloride solution, unimmunized guinea pigs all died of tetanus within forty-eight to seventy-two hours; but that if these pigs had been immunized and their blood

CHART I

COMPARISON OF RESULTS OBTAINED BY SEVERAL WORKERS

Antitoxin Units in 1 cc. of Blood	*Ramon and Zoeller (1933) (a)*	*Formol Toxoid* *Sacquepee (1933) (b)*	*Hall (1937) (c)*	*Sneath and Kerslake (1934) (d)*	*Alum Precipitated Toxoid* *R.A.M. College (e)*	*Bergey and Etris (1936) (f)*	*Gold (1937) (g)*	*Hall (1937) (h)*
0.01		3		3				
0.01 to 0.1		107	11	6	3		1	
0.1 to 1	Most cases	126	1	20	21	14	13	12
1 and over	A few cases	1			6	16	4	1

(a) Exact numbers not quoted. 1st dose, 1 cc.; 2nd dose, 30 days later, 1.5 cc.; 3rd dose, 10 to 15 days later, 1.5 cc.; tested about 1 month later.

(b) 1st dose, 1 cc.; 2nd dose, 20th day, 2 cc.; 3rd dose, 30th day, 2 cc.; tested about 6 months later.

(c) 1st dose, 1 cc.; 2nd dose, 6 weeks later, 1 cc.; 3rd dose, 2 weeks later, 1 cc.; tested 6 weeks after 3rd dose.

(d) Dosage and test as in (a).

(e) 2 doses of 1 cc. at intervals of 6 to 7 weeks. Tested about 1 month later.

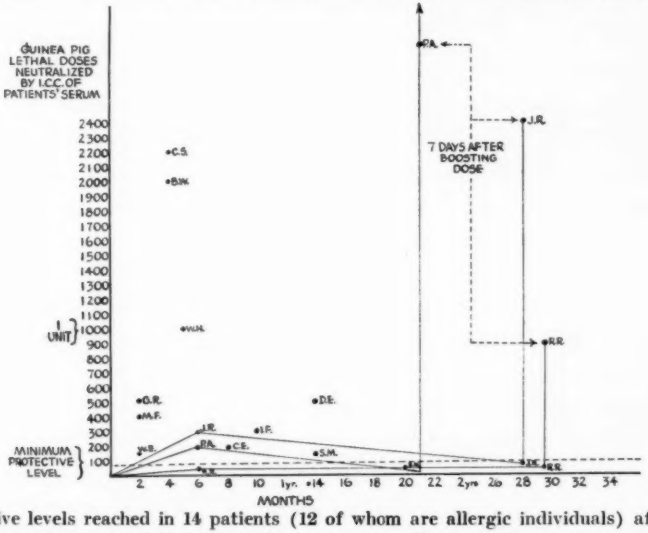
(f) 2 doses of 1 cc. of alum precipitated toxoid separated by an interval of some months. Tested 1 month after 2nd dose.

(g) 2 doses of 1 cc. of alum precipitated toxoid at intervals of 92 days. Tested from 7 to 15 days after 2nd dose.

(h) 2 doses of alum precipitated toxoid at an interval of 6 weeks. Tested about 6 weeks after 2nd dose.

CHART II

IN CHART II ARE SHOWN THE PROTECTIVE LEVELS REACHED IN FOURTEEN PATIENTS AFTER ADMINISTRATION OF TETANUS TOXOID



Protective levels reached in 14 patients (12 of whom are allergic individuals) after two 1 cc. doses of alum precipitated toxoid given two months apart, the curves are approximate immunity curves for 3 cases.

titre showed 0.01 unit or more, 87 per cent remained completely protected and 13 per cent showed mild tetanus from which they recovered. A group of mice showing 0.1 unit or more were completely protected against 100,000 spores. It would seem then that 0.1 unit is a safe minimum level to accept and is probably much larger than is necessary to protect against infection resulting from trivial wounds. Whether this level is sufficient for protection against massive infection is not known.

What dose and what spacing of doses should be used to produce the minimum level? It is generally conceded that the alum precipitated preparation should be used. The reactions are few and very rarely general, usually local soreness with very little discomfort. Two 1 cc. doses given sixty to ninety days apart appear to give the highest titre. Usually about seven to ten days after the second dose the titre has risen to over 0.1 unit per cc. even if this second dose is given as long as two years after the first dose. We may say that very adequate immunity then develops certainly by fourteen days after the second dose and in most cases by seven days.

How long does the active immunity last at the minimum protective level or above?[16] It varies considerably. It has disappeared within ninety days after the second injection and has lasted as long as two years. The basal immunity upon which a secondary stimulus may be had is probably lifelong.

A crucial question is, whether the boosting dose given months or years later, after the level in the blood has fallen to well below the accepted minimum protective level, will be effective. In America there is now ample confirmation of Ramon's work. Hall,[13] from his studies in the Navy, concluded that no matter what interval was used in the basic courses or how low the level of antitoxin at the time of the final or secondary stimulus, the antitoxin titre rose in seven days or less to highly effective levels. In one week after a boosting stimulus given one year after the immunization, Jones and Moss[7] found that all but one had a blood level comparable with that following the old prophylactic injection. These results are analogous to those published by Sneath and Kerslake.[11]

Cowles[17] at Yale endeavored to find out just how quickly his boosting dose acts. Twelve men immunized one year previously and having titres ranging from 1/50 to 1/5 unit of antitoxin per cc. received 0.5 cc. of alum precipitated toxoid subcutaneously. Six of these when tested on

the third day after the toxoid administration failed to show any significant increase in titre; of eight tested on the fourth day, four responded; of eight tested on the fifth day, all had 1/20 unit of antitoxin or more. By the seventh day all had reached 1/2 unit or more with the exception of one man who had only 1/20 unit. The duration of this higher immunity after a repeat dose is not known. Gold[14] states that it may fall below 1/10 unit in three to six months. According to Sneath and Kerslake[11] a secondary stimulus of plain toxoid seemed to produce a more lasting immunity. Further work must be done on this point.

Certain theoretical considerations should be mentioned. It seems reasonable to believe that, given a certain immune level induced by active immunization, this level would be raised by the stimulus of an active infection. A person whose immune mechanism was set to combat tetanus by previous active immunization would show a rapid response to the production of toxin by the infection, just as that same person would show a rapid rise in immune level as the result of a boosting dose of toxoid. This type of response would occur, we assume, provided that the infection produced enough toxin to leave some toxin free and unneutralized by antibodies already existing in the body. Wolters and Dehmel[18] showed that guinea pigs can react this way. They inserted into immunized animals splinters infected with tetanus spores and found that these animals did not develop tetanus but did show appreciable elevation in protective titre. We can reason also somewhat by analogy from immune reactions in individuals previously immunized against diphtheria. There is some evidence to show that the amount of toxin in a Schick test is sufficient to stimulate increased antibody production. More work needs to be done to confirm this very important matter.

Conclusions

We may now ask: what facts are well enough substantiated to rely on? How far may we apply them?

It has been shown that two doses of 1 cc. each of alum precipitated toxoid given two or three months apart or three doses of plain toxoid 1 cc., 1.5 cc., 2 cc. at three week intervals will in seven, at the outside fourteen, days after the last dose produce a blood level as high or higher than 1500 units of the old antitoxin. A boosting dose given one to several years later will bring this level back to a protective level and often far above in seven days in almost every case tested.[19,20,21,22] The reactions

to these toxoids are slight. The alum precipitated toxoid is quite thermostable and therefore keeps well.

To be able to rely absolutely on immunization by toxoid the following things should be done:

1. A blood titration test should be made two months after the last immunizing dose (laboratories are now equipped or can soon be equipped to do this).
2. If injury requiring protection occurs any time after three months after immunization, a boosting dose should be given within twenty-four hours of injury.
3. Even this should not be relied on in cases of very extensive injury such as would require gas bacillus prophylaxis or injuries where there was extensive hemorrhage. In these cases antitoxin should be given also.

Tetanus rarely develops before five days but it is in this type of case that the incubation is likely to be early. The usual incubation is between seven and fourteen days.

Who *should* receive active tetanus immunization?

1. First of all I place those who are sensitive to horse serum. That means, of course, those who have had severe and moderate serum reactions from previous serum injections.
2. Asthmatic patients.
3. Other allergic individuals if they are in occupations or indulge in avocations that carry with them danger of injury.

It is justifiable to give tetanus immunization to the following optional groups:

1. Children, especially those living in the country or those who ride. Statistical analysis shows that most of the cases of tetanus at present occur from trivial injuries. These cases would very definitely be prevented by such prophylaxis whether a blood titration was made or not.
2. Individuals, non-allergic, engaged in hazardous occupations or avocations.

The author is greatly indebted to Mr. Charles K. Greenwald, Bureau of Laboratories, New York City, for doing the laboratory work on the cases reported.

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THE INFLUENCE OF EMOTIONAL FACTORS UPON PHYSIOLOGICAL AND PATHOLOGICAL PROCESSES*

FRANK FREMONT-SMITH

THE increasing pace at which new knowledge in the basic sciences is being applied to the solution of clinical problems, together with the widespread demand for health-care by a public better informed than ever before, has created new and urgent problems for medical education and for medical practice. As we survey the present situation in an effort to foresee changes in the teaching and practice of medicine which the future must surely bring, we may well ask whether in the swiftness of our advance we may not have lost something of the wisdom of the past; whether the new and revealing laboratory techniques have not focussed attention too exclusively upon organs and parts of organs to the neglect of the whole, upon disease processes to the neglect of the individual who is diseased. Francis W. Peabody[1] said: "What is spoken of as a 'clinical picture' is not just a photograph of a man sick in bed; it is an impressionistic painting of the patient surrounded by his home, his work, his relations, his friends, his joys, sorrows, hopes and fears." And Hippocrates[2] before him taught that "the nature, even of the body, can only be understood as a whole." Is there something in this philosophy which is not included in the modern approach to medicine? Was a better knowledge of the whole perhaps the secret of the much mourned family physician who in the course of years came to know the life history of his patients and of their families and could evaluate the present illness in the light of such perspective?

That the medical profession is becoming increasingly aware of this question is evidenced by the frequency with which the medical student is admonished to look upon the patient "as an individual" and view him "as a whole." But unless this viewpoint is applied in fact to the individual patient, it becomes a mere abstraction with little meaning at the bedside,

* Read December 2, 1938 in the Friday Afternoon Lecture Series of The New York Academy of Medicine.

where we are too apt to focus the best laboratory procedures on the depersonalized "case."

Is not the public, nearly all of whom sooner or later become our patients, beginning to feel a certain dissatisfaction with modern medical practice, even when skilled specialists are available to study the dysfunction of this organ or of that, and physical examinations and laboratory tests are far more revealing than in the past? Why is it that a viewpoint, accepted by the ancients, sensed by the country doctor, and enunciated by the present leaders of our profession, should still elude us in daily practice? The answer lies partly in the inadequacy of the technique of history taking, to which we shall return later, and partly in the focus of the physician's interest. To the family doctor the patient is usually no stranger when he seeks advice. Often the physician has known him since childhood, and quite naturally takes into consideration his previous illnesses, personality and family background, so that the patient's symptoms are seen in the perspective of the life history of the individual. The modern physician, on the other hand, rarely sees the same patient through the years. With many technical devices at his command, he tends to become preoccupied with the function of organs and organ systems which can be measured with ever increasing accuracy. But this alone does not satisfy the patient whose primary interest is in himself – the sick man.

It is not my purpose to discuss the need of studying the individual patient, his emotional tensions, peculiarities and prejudices, in order merely that we may know how best to gain his confidence, nor merely that we may deal with overt emotional crises or be ready on occasion to play the role of father confessor. There is another more cogent reason why the modern doctor, whether he be general practitioner or specialist, can no longer afford to overlook the personality pattern and emotional responses of the individual patient. For in the patient's personality structure, in his way of reacting emotionally or of failing to react to his environment are to be found the factors which not only lie at the root of the so-called "functional" disturbances but which also often determine the onset, severity, duration, exacerbations, and even the outcome of disease.

The physician today is not satisfied with the diagnosis when, in the case of an infectious disease, the infecting agent has been identified. He wants to know both the source of the infection and the nature of the immunological disturbance which made infection possible. We have

progressed beyond the stage where simple cause and effect relationships are sought. The biochemical changes taking place in the patient are as important as the nature of the invading organism for the production of disease. Similarly, when a gastric ulcer has been accurately described by x-ray and gastroscope, the diagnosis should be considered still incomplete until we have investigated the factors which lead to exacerbations of symptoms and threaten hemorrhage or perforation. If the symptoms are accentuated by family quarrels, this fact should be included in the clinical picture. Its neglect may prevent a cure. If hospitalization of an ulcer patient is more effective because it removes the patient from the scene of the quarrels than because it allows strict regulation of the diet, this also should be understood by the physician. Obviously in such case, proper therapy must include either a change in the home situation or in the patient's attitude toward it.

In order to understand how emotional factors can influence the process of disease it will be helpful to review briefly the anatomical, physiological and biochemical mechanisms which are normally activated during emotional stress. Walter B. Cannon[3] in his classic studies on emotional excitement has shown clearly the profound changes occurring in animals during rage and fear, i.e., the elevation of the blood pressure, the diversion of the blood flow from skin and splanchnic regions to muscles, heart and brain, the inhibition of gastric function, the pouring into the blood of glucose, and of adrenalin – all evidences of pronounced activity of the sympathetic division of the autonomic nervous system. Recently Morris Bender,[4] while working in John F. Fulton's laboratory at Yale, and now at the Mount Sinai Hospital, has presented evidence that acetylcholine as well as adrenalin is secreted into the blood in cats and monkeys during fear, showing that the parasympathetic as well as the sympathetic division of the autonomic nervous system may be thrown into activity during emotional excitement. This evidence of parasympathetic action fits in well with a number of clinical phenomena, as indicated by Kling,[5] such as blushing, lacrimation, fainting, vomiting, involuntary urination or defecation; any of which may occur under intense emotional stress, and which cannot be readily understood on the basis of sympathetic stimulation alone.

Since the autonomic fibers are widely distributed throughout the organism to skin, blood vessels, viscera, reproductive system, special sense organs, kidneys, the glands associated with the gastrointestinal

tract and the endocrine glands, which pour their secretions into the blood stream and thus influence distant organs, it is evident that activity of the autonomic nervous system, either directly or through the mediation of the blood stream, may be expected to have an influence upon the function of practically every organ and tissue. There is no valid reason why a diseased organ should escape such influence; on the contrary there are striking examples of pathological states which render an organ oversensitive to autonomic stimulation. For example, in Raynaud's disease the blood vessels of the affected part become overresponsive to sympathetic stimulation, while in hyperthyroidism the heart, as well as other tissues, overreacts to adrenalin injection as well as to emotional stimulation.

The autonomic nervous system has intimate connections with the central nervous system on both the efferent and afferent side. Recent studies, admirably reviewed in Fulton's[6] *Physiology of the Nervous System,* have made it evident that the hypothalamus is the chief center for the integration of impulses to and from the autonomic system, and that intimate connections exist between the hypothalamus, the thalamus and the cerebral cortex. Stimulation* of the posterior and lateral nuclei of the hypothalamus in animals produces diffuse discharge of all divisions of the sympathetic system, causing acceleration of the heart, dilation of the pupils, inhibition of peristalsis of the gastrointestinal tract, pilomotor activity, rise in blood pressure, increase in respiratory rate and decrease in bladder tonus. Stimulation of the middle nuclei, however, results in responses of an opposite type, being in general characteristic of parasympathetic activity. Thus the heart rate is slowed and the auriculoventricular conduction time is increased, there is increase in peristalsis of the stomach, and increase in tonus of the bladder. A fall in blood pressure can be produced by stimulation of the anterior region of the hypothalamus. That these two types of response to stimulation of the hypothalamus are mediated by the sympathetic and parasympathetic nerves respectively is proved by the fact that the appropriate responses cannot be obtained after section of sympathetic, or of parasympathetic nerves, as the case may be. Experimentally produced lesions in the hypothalamus lead to disturbances of heat regulation, of water regulation, of carbohydrate and fat metabolism, and of sexual function. Finally, the outbursts of rage which occur spontaneously or are readily elicited in animals after

* For references to this and the following experiments on the hypothalamus and the cortex, *vide* Fulton.[6]

decortication disappear when the posterior area of the hypothalamus is destroyed. These pseudoaffective outbursts, called "sham rage" by Cannon and Bard, are accompanied by signs of widespread sympathetic activity, indicating the intimate relation between affective discharge and activity of the autonomic nervous system.

The release of exaggerated emotional expression and autonomic activity by decortication implies a cortical inhibition or regulation of these functions but, as Fulton[6] has said, it is only within the last few years that the extent to which the cerebral cortex influences the autonomic nervous system has become obvious. In the cat and monkey, stimulation of discrete areas of the cortex will evoke marked elevations in blood pressure, while stimulation of neighboring areas results in a fall in pressure. The rise in pressure is accompanied by acceleration of the heart, while the decrease in pressure is associated with slowing of the heart rate. These responses demonstrate both a sympathetic and a parasympathetic representation in the cortex, since the rise in blood pressure and increase in heart rate are diminished although not wholly abolished by section of the splanchnic nerve and removal of the stellate ganglia on both sides, while section of the vagi abolishes the lowering of blood pressure and the slowing of the heart.

As further evidence there may be cited the experiments of Green and Hoff[7] on cats and monkeys which indicate that in the motor and premotor areas of the cerebral cortex there exists a mechanism for diverting the blood from visceral to muscular bed, which is mediated through the peripheral nervous system. Thus stimulation of the cortex may produce physiological changes analogous to those which occur spontaneously in rage or fear. Stimulation and ablation experiments have demonstrated the cortical control of sweating, as well as the absence of the psychogalvanic reflex on the contralateral side when a sharply localized area of the cortex is removed. Dilation or constriction of the pupil, as well as lacrimation and salivation, may be provoked by cortical stimulation. Ablation of the frontal lobes produces motor hyperactivity of the stomach with pyloric spasm, while stimulation of the frontal cortex also influences gastric peristalsis. The "psychic" flow of gastric juice is dependent upon cortical function, and micturition is also partly under cortical control.

Thus we may make a rough sketch of the intricate organization of the autonomic nervous system, its integration in the hypothalamus and

regulation in the cerebral cortex where there exist both sympathetic and parasympathetic representation. The organism is prepared for instant and violent action and yet so regulated that whether at rest or in action, its internal environment is kept within those limits of relative constancy which are essential for efficient activity and even survival.

The inward nature of affective experience still eludes us. The James-Lange theory of the emotions has been discarded, and a satisfactory formulation will probably have to await more precise information on both the clinical and experimental side. It may be stated, however, that affective states, although often evoked by sensory stimuli, are dependent primarily upon central rather than upon peripheral activity; that the gross patterns of emotional expression are organized subcortically, since decortication leads to their release in exaggerated form; and finally that the pathways for such nervous discharge are via the hypothalamus into the autonomic nervous system. The ultimate action of the autonomic nervous system, and hence of emotional activity, upon the tissues of the body is brought about by the chemical mediators adrenalin and sympathin released by sympathetic stimulation, and acetylcholine released by activity of the parasympathetic nerves and probably by other hormones, whose secretion or discharge into the blood stream may be influenced by activity of the autonomic nervous system. Since adrenalin and acetylcholine, both highly active physiologically, may be found in the blood stream simultaneously under fear reactions, and since fear may be accompanied by symptoms due to sympathetic or parasympathetic activity, or both, it seems probable that the sympathetic and parasympathetic divisions are stimulated nearly simultaneously in the homeostatic regulation of the organism. Whether the symptoms resulting from emotional stress are predominantly sympathetic or parasympathetic may then depend either upon the relative intensity of the stimulation of these two divisions, or upon hyper-reactivity of an organ or tissue. Among the causes of such local hyper-reactivity are various pathological processes. Such is the system, anatomical, physiological and biochemical through which emotional activity is expressed.

In Dunbar's volume, *Emotions and Bodily Changes*,[8] there is reviewed a vast but scattered literature dealing with these psychosomatic problems. Here may be found many striking case histories illustrating the influence of emotion upon disease, cases involving nearly every organ of the body. Almost every physician with whom this topic is

discussed will remember one or two dramatic instances. As Dunbar points out, however, few systematic studies have been made. Until this is done, using effective diagnostic methods, we cannot know how many such cases are being missed.

One important reason why the role of emotional factors is overlooked in many cases is because in history taking we assume that the patient will remember accurately and thereby ignore the power of his "forgettory" (Wile[9]). We are inclined to think of remembering as an active process and tend to overlook the fact that we could not focus our memory upon an incident or object unless we had an efficient mechanism for excluding at that moment all the other memories which might crowd in upon us. Forgetting often must be looked upon as an active process, not just an absence of remembering. In fact the vigor with which we are able to forget is at times appalling!

It is common knowledge that when an old memory is revived by some appropriate stimulus, not only is the original experience remembered, but the emotions associated with it are also reawakened and felt, often with intensity. What is less well known, but even more important for the physician, is the fact that the stimulus may sometimes fail to bring to conscious memory the old experience, and yet reawaken the emotional feeling and the concomitant activity of the autonomic nervous system. Under such circumstances the individual may realize that he is frightened or angry but wrongly attribute the feeling to something in the present situation, failing to realize that its source is in an only partially awakened memory.

In some instances of partly evoked memories, the emotion may not be recognized as such, only the symptoms due to autonomic activity coming into consciousness. The individual notices a pounding of his heart, or perhaps feels nauseated and vomits, but remains unaware of fear in the first instance, or of disgust in the second. If the heart, digestive system, or any other organ is especially sensitive to autonomic activity, or is already the site of disease, then it is not difficult to see how the arousing of emotional tension, can lead through activity of the autonomic nervous system to serious symptoms and to the extension of the pathological process. For instance, a patient with a chronic peptic ulcer had three severe hemorrhages from the ulcer each occurring within twenty-four hours of an emotional crisis. Here may be cited also the recent observation of Bruenn[10] that anxiety causes an increase in the auriculo-

ventricular conduction time, as shown by the electrocardiograph, in patients with rheumatic fever.

Since the patient has often completely forgotten the information needed by the physician to determine the importance of emotional factors in the illness, or if he remembers the disturbing factors, has forgotten their association with the onset of symptoms, the direct question-answer technique of history taking will almost inevitably fail to reveal the emotional tension or its relation to the illness. The patient cannot be expected to tell what he has forgotten; what, because of its disturbing nature, has been excluded from conscious memory. But since anxiety in one form or another is usually at the root of evasion or of repression of emotional problems, an essential factor in aiding the patient's memory is the establishment of confidence in the doctor.

In the presence of disease, how can we determine whether emotion plays a significant role? The diagnosis of "functional disturbances" formerly was made by exclusion of discoverable organic processes; but this is both difficult and inadequate. Moreover, the arbitrary distinction between "organic" and "functional" is more misleading than useful. We need criteria for the positive diagnosis of the role of emotion in illness. Among such criteria is a time relationship between an emotional crisis and the onset of symptoms. The positive diagnosis is considerably strengthened if several exacerbations of symptoms, or attacks have been immediately preceded by recurrence of the same or similar emotional conflicts. If the patient fails to recognize any connection between the emotional tension and the symptoms, and particularly if the patient has completely forgotten the emotional crisis or its time relationship to the onset of the symptoms, then the role of the emotion as an etiological factor in precipitating the symptoms is rendered highly probable.

The intellect is expected to govern the emotions; the cerebral cortex to regulate the activity of the lower centers; but intellect is often powerless before emotions which have been forgotten, for the lower centers may then discharge with an uncontrolled intensity, and often with a stereotyped pattern, which is reminiscent of the behavior of the decorticated animal.[11] This suggests that the exclusion from consciousness of the memory of an emotionally disturbing event may be analogous to a partial temporary decortication. In such circumstances the return to conscious memory of the forgotten experience may lead to an abrupt decrease in activity of the autonomic nervous system and prompt

cessation of the accompanying symptoms.

This sequence of events was reproduced in man by F. Deutsch and E. Kauf[12] in 1923, who set out "to show experimentally that ideas and experiences originally accompanied by anxiety but long since forgotten, are the cause of disturbances in the cardiovascular system." I quote from Dunbar's review[8] of their article:

" 'An exciting experience was suggested to the subject in hypnosis, with the simultaneous suggestion of complete amnesia for it. Furthermore, the posthypnotic suggestion was given that with a certain signal (seemingly accidental showing of a handkerchief) the subject would have the same sensations as during the experience. When, after hypnosis, the handkerchief was shown, there was in all cases a definite increase in pulse rate (maximum 27 beats per minute), similar to that during the suggestion of the experience in hypnosis.' This shows, the authors say, that an experience which is no longer in consciousness may produce the same sensations as at the time of its first happening. * * * Two subjects were given, in addition, the suggestion that on the dropping of the handkerchief they would remember the experience completely. Whereas on production of the handkerchief there were pulse accelerations of 15, 12, 13 beats per minute in one case, 22 and 27, in the other, repetition of the stimulus after dropping of the handkerchief produced no, or only negligible, acceleration. Especially in one case there was intense anxiety with recollection of the experience."

These experiments illustrate that an emotionally disturbing experience induced and forgotten under hypnosis on awakening may lead to exaggerated response when partially reactivated. In a similar way an individual with pent up but unrecognized anxiety may be thrown into a state of terror by an experience, such as a barely-avoided automobile accident, which would ordinarily evoke but slight fear. The resulting terror, which may persist for some time, is absolutely real to the individual and may cause him to misjudge the actual danger in the present situation. In some cases only a very specific stimulus, one closely connected with the forgotten experience, is able to release the repressed emotion. In other instances, as in a vivid radio broadcast at a time when war seemed imminent, widespread panic may be produced in a group of people with very different past histories, provided there is sufficient underlying anxiety in the group.

The problems associated with repressed emotion are the problems of

human unhappiness, bereavement, insecurity and despair. For many of these civilization has as yet no adequate answer. Not infrequently, however, that aspect of the problem which affects the patient's health, may be improved by common sense advice; while just the opportunity to talk it out with another human being often throws a new light upon the issue and changes the patient's attitude towards it. This may be all that is necessary. Often the fact that the physician listens without censure to an account of the patient's mistakes and sorrows, does much to restore the patient's self-respect and gives him the needed courage to make his own decisions.

In the more serious emotional problems and personality disorders, the physician should turn to a neuropsychiatrist, but much may be accomplished by the general practitioner and by the specialists in other fields, once the problem has been revealed.

In closing I should like to emphasize two points: first, that organs and tissues which are the site of disease are not immune to the physiological and biochemical effects of emotional conflict, and second, that the most important conflicts in this respect are often those which the patient has forgotten.

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THE ROLE OF THE NEW YORK ACADEMY OF MEDICINE IN THE DEVELOPMENT OF THE AMERICAN MUSEUM OF HEALTH*

GEORGE BAEHR

THE New York Academy of Medicine and the medical profession of the City of New York have long had a deep and active interest in the establishment of a Museum of Medicine and Public Health in this city which might serve the City, the State and the Nation. Although many have recognized the need, special credit must be given to Dr. D. Bryson Delavan, a distinguished physician of this city, who persistently and ardently advocated its consideration over a long period of years. By 1927 his persistence had convinced Dr. Linsly R. Williams, then director of The New York Academy of Medicine, that the initiation of this project was one of the public responsibilities of the Academy.

In the year 1927, the Council of the Academy authorized the President of the Academy to appoint a special committee for the purpose of studying and stimulating the establishment of such a museum. The first committee appointed in 1928 included Dr. Williams, Dr. B. Sachs, Dr. John A. Hartwell and Dr. E. H. L. Corwin. In 1933 a larger special committee on museum was created of which I have had the privilege of serving as chairman. It was hoped that the gradual accumulation of material for the proposed museum might ultimately result in encouraging the interest and the financial support of philanthropic foundations, of people of means and of the municipality. In the absence of more adequate storage and exhibition space in the Academy building it was decided to restrict the collection at first to material having a bearing upon the history and development of medicine. The main purpose, however, was not neglected, namely, to interest both governmental and private support for a museum of medicine and public health to serve the medical profession and the public. With this idea in mind, a conference was held at the Academy in 1931 between the Academy's Committee on Public Health

* Address delivered at the dedication of the Medical and Public Health Building of the World's Fair, New York, June 17, 1939.

Relations and representatives of the American Public Health Association in the hope that these two organizations might collaborate; and when Rockefeller Center was under construction there was some hope for a time that space might be provided.

At that time we had in mind a museum which would combine the best elements of the popular Hygienic Museum of Dresden with which I had been impressed in 1912 and the more scientific Wellcome Museum of London. It was our belief that, like New York's Museum of Natural History, a popular museum for health education must have the best professional leadership and a substantial scientific working background so that it might maintain the highest standards of scientific accuracy and progress and not degenerate into mere cheap and unmeritorious showmanship.

Five years ago, shortly after the inauguration of Mr. LaGuardia as Mayor of the City of New York, I had an opportunity to bring this subject to his attention. With his usual quickness of perception, he immediately grasped the significance to health education of a great museum, like our Museum of Natural History but devoted to problems of health and disease. Sometime in 1935, I was again called to see him. He told me in confidence of the news which had not yet been made public, that a World's Fair in New York City was under consideration. He reminded me of our previous conversation concerning a museum of medicine and public health and asked me to prepare a short brief on the subject which he might advance as one of the worthy reasons for holding a World's Fair in New York. It was his idea that a great non-commercial exhibit on medicine and public health should be created in such a manner and so comprehensively that it might serve as the nucleus for the future permanent museum which I had proposed to him. In this way, he suggested, our hopes might come to realization at the termination of the Fair in 1940, far sooner than we had dared to hope.

I then consulted with the officers of the Academy of Medicine and with Dr. Louis I. Dublin, recently president of the American Public Health Association. At his instigation, Dr. Victor Heiser and Mr. Homer Calver of the American Public Health Association met with me and assisted in preparing the brief. This brief and the continued interest of Mayor LaGuardia and Mr. George McAneny resulted in the appointment of the small working committee which developed this great project, the Medical and Public Health Building of New York's World Fair,

which we dedicate today, with the self sacrificing assistance of several hundred experts in all branches of medicine and public health. The composition of this small executive committee indicates how successful has been the collaboration of the three major participating interests, the City of New York, the medical profession and the field of public health. The interest of the City is represented on the committee by the Commissioners of Health and of Hospitals, the public health association by three representatives, the medical profession by four representatives, among whom I have had the privilege of representing The New York Academy of Medicine. The board of directors of the permanent American Museum of Health is now composed in a similar fashion, except that it includes distinguished citizens in addition to the city government and the major local and national organizations representing public health and medicine.

I speak not only on behalf of The New York Academy of Medicine, but also for the entire medical profession of the City of New York and for its five medical schools in assuring you of our continued devotion to this great enterprise. We fervently believe that it will be the center from which will emanate the developing techniques of health education for the people of our City and the Nation. To this center will come hundreds of physicians and public health officers for training in the modern methods of health education, and it will share its accumulating store of rich experience and its wealth of technical material with all the health and welfare agencies of the land.

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"Possession does not imply approval"

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DEATHS OF FELLOWS

COHN, FELIX: 945 West End Avenue, New York City; born in Vienna, Austria, June 24, 1860; died in New York City, June 2, 1939; received the degree of Bachelor of Arts from the College of the City of New York in 1879; graduated in medicine from the University of Heidelberg, Germany, in 1884; elected a Fellow of the Academy April 3, 1890.

Dr. Cohn had been consulting laryngologist and otologist to the Montefiore Hospital since 1912, the Lenox Hill Hospital since 1925 and the Beth Israel Hospital since 1930. He was a Fellow of the American Medical Association, a member of the American Academy of Ophthalmology and Otolaryngology, and the County and State Medical Societies.

Dr. Cohn was the author of numerous publications on the ear, nose and throat.

TWELFTH GRADUATE FORTNIGHT

OCTOBER 23 TO NOVEMBER 3, 1939

Arrangement of Afternoon Hospital Clinics

Monday	October	23	Babies and Bellevue
Tuesday	October	24	Memorial and New York
Wednesday	October	25	Montefiore and Post-Graduate
Thursday	October	26	Mount Sinai and New York
Friday	October	27	Lenox Hill and Mount Sinai
Monday	October	30	Bellevue and Presbyterian-Neurological Institute
Tuesday	October	31	Montefiore and St. Luke's
Wednesday	November	1	Joint Diseases and Lenox Hill
Thursday	November	2	Morrisania and Post-Graduate
Friday	November	3	Sloane and Woman's